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EDITORIAL

Towards evidence-based integration of services for HIV, non-communicable diseases and substance use: insights from modelling

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The year 2020 is the designated date for achieving the Joint United Nations Programme on HIV/AIDS 90-90-90 targets for human immunodeficiency virus (HIV) diagnosis, treatment and viral suppression [1]; it also marks completion of one-third of the time allotted (from 2015 to 2030) for achieving the Sustainable Development Goals and the corresponding end of acquired immune deficiency syndrome (AIDS) [2]. Yet the HIV epidemic is far from ended: nearly two million people still acquire HIV infection every year, the number of people living with HIV (PLHIV) continues to increase and new infections are still on the rise in many populations [3]. To date, the response to HIV has largely been an "exceptional" one, with dedicated funders (most notably the President's Emergency Plan for AIDS Relief) tending to build new structures rather than strengthening the underlying health systems [4]. By some measures, this approach has been exceedingly successful, resulting in over 21 million people receiving antiretroviral therapy (ART) and a corresponding reduction in AIDS mortality [3]. But it is also an approach that may require modification in the coming decade, with progress towards Sustainable Development Goals underway and a concomitant focus on Universal Health Coverage (UHC) emerging [5].

Given the ambitious joint goals of ending AIDS while also achieving good health and wellbeing for all people, it may be instructive to consider the population-level epidemiologic and economic consequences of the different ways in which services for HIV and other conditions can be integrated, in the context of broader health systems [6]. This Supplement presents a set of articles that explore the potential role of mathematical modelling to address this need.

These articles help illustrate that the concept of "integrated HIV services" itself is not – and need not be – uniform across all situations. For example in settings with generalized HIV epidemics, non-communicable diseases (NCDs), such as cardiovascular disease (CVD) and cancer, are exacting an increasing toll of morbidity and mortality as populations living with HIV age. As such, implementing routine (or even expanded) diagnostic testing and screening for some of these conditions among PLHIV could be an important step forward in certain settings [7]. In contrast, in settings where HIV is concentrated among people who inject drugs (PWID) and thus overlaps strongly with hepatitis C and risk of drug overdose, integration of HIV services with substance use services and hepatitis C treatment programmes might be the overriding priority [8]. In some settings, services for certain other conditions may be well established, such that integrated care might consist primarily of forming linkages between these services and those for HIV, enabling PLHIV to "link out" and thus access more comprehensive care. In other settings, however, services for other conditions may be more rudimentary, and an important dimension of integration could be in the utilization of HIV facilities to strengthen care for PLHIV while also providing some amount of care for HIV-negative persons. Regardless of how "integrated HIV services" are conceptualized, integration has the potential to effect synergistic benefits by achieving economies of scope, using the same infrastructure to provide multiple services. Because of this potential benefit, integration of HIV and other services merits careful evaluation.

The articles in this Supplement examine a specific set of issues and perspectives around integration of services for HIV and other conditions. In particular, these articles focus on (1) integration of HIV care with services for NCDs, especially CVD, in settings with a high "dual burden" of HIV and CVD, and (2) integration of HIV and substance use services in populations that can benefit from HIV prevention and treatment as a package that also includes services for substance abuse. Although each individual article addresses a narrowly defined topic, these articles collectively provide important insight into some of the potential epidemiological and economic consequences of moving towards more integrated HIV services. They also illustrate that the landscape of integrating HIV services into broader health systems – and integrating broader

healthcare services into HIV-specific systems – is one that is only beginning to take shape; the need for additional data and corresponding analysis to inform specific policy decisions is urgent.

INTEGRATION OF HIV AND NCD/CVD CARE IN HIGH-BURDEN SETTINGS

Kibachio *et al*. [9] use the example of HIV/NCD care in Kenya to highlight some of the key considerations that must be taken into account when modelling the integration of HIV and other services. These authors demonstrate how models can provide support throughout the policy-making process – from estimating disease burden to elucidating policy options to forecasting comparative epidemiological impact, cost-effectiveness and budget impact of different potential decisions. Similarly, Kintu and colleagues [10] discuss opportunities, challenges and trade-offs of integrating NCD and HIV services in sub-Saharan Africa from a policy perspective – including potential increases in efficiency from leveraging HIV platforms to address NCD management, reductions in quality due to overburdened healthcare staff, potential inequalities given the large burden of NCDs in the general population and the need for additional funding to support integration of services. While highlighting potential pitfalls, both papers hypothesize that the benefits of integration may often outweigh the risks in high-burden settings – and they provide a roadmap for how quantitative models and innovative policy making can support the process of examining these trade-offs.

This hypothesis of a favourable risk-benefit balance is tested in three modelling papers that seek to determine if adding CVD care to existing HIV services would be an impactful and/or cost-effective use of resources. Kasaie *et al*. [11] consider screening PLHIV for hypertension and diabetes in the context of outreach campaigns and HIV treatment in the Sustained East Africa Research in Community Health programme in Kenya [12], and Sando *et al*. [13] consider screening persons on ART in Uganda for hypertension, diabetes and high cholesterol and initiating treatment for these conditions where indicated. Both papers find that such programmes may be cost-effective in circumstances when the costs of CVD treatments are low, effectiveness is high and persons receiving services are otherwise at elevated risk of suffering ill effects of CVD.

While integrated HIV/NCD programmes may be cost-effective in some settings, the costs of treatment for PLHIV on ART may be high due to contraindications between common medications for NCDs and ART. A third analysis, by Boettiger *et al*. [14], presents such a counterexample. These authors use data from the TREAT Asia HIV Observational Database to inform a 20-year simulation of adults receiving ART in Thailand. In this simulated cohort, they estimate that the cost of providing statin therapy to reduce the risk of CVD events would be high compared to its effect. As a result, very large reductions in the cost of those statins would be needed for such an approach to be considered cost-effective under thresholds that are currently thought to be realistic.

The cost and budget impact of an alternative model – of expanding NCD care for all persons in HIV and acute health clinics more generally (i.e. not in a manner that stems solely from HIV platforms) – is estimated in another paper in this Supplement, by Osetinsky *et al*. [15]. The authors argue that costs of expanding NCD care in western Kenya can be mitigated by growing capacity in existing clinics without NCD services, strengthening referral systems and task shifting between healthcare workers with different levels of training. The costs of expanding NCD care in this study were relatively modest on a per-visit or per-facility basis, but a comparison to current conditions is difficult because the health benefit and opportunity costs of this expansion are uncertain. The authors note that a major challenge in the status quo "unintegrated" approach is patients' out-of-pocket expenditure to attend clinic visits, especially for patients who would not otherwise make these trips. As noted by both Osetinsky *et al*. and Kibachio *et al*., this represents an argument in favour of prioritizing NCD management for PLHIV, who unlike the general population must already make frequent clinic visits while on ART.

As a whole, these analyses provide support for the principle of leveraging the HIV care platform to offer more services, but they also point towards the need for specific strategies to be evaluated in practice. Notably, none of these modelling papers tackles the question of equity, in that prioritization of NCD care for PLHIV may disproportionately benefit those who already have better access to care. Nor do they compare these strategies for integrating NCD and HIV services against other major elements in the movement towards UHC, such as providing PLHIV with an evidence-based Essential Health Package – a package that would make certain essential services universally available while limiting services without sufficient evidence for effectiveness or cost-effectiveness [16].

INTEGRATION OF HIV AND SUBSTANCE USE SERVICES

As examples of contexts in which integration of services for key populations can form a potentially synergistic package of comprehensive care, two mathematical modelling studies in this Supplement examine intersections between HIV and substance use in Latin America. Cepeda *et al*. [17] model a range of scenarios in which ART and harm reduction services are scaled up among PWID in Tijuana, Mexico, predicting the impact that concomitant scale-up could have on the incidence of both HIV and overdose. In contrast, Bórquez *et al*. [18] focus on stimulant use and HIV among men who have sex with men and transgender women in Lima, Peru, exploring the impact of HIV pre-exposure prophylaxis and harm reduction interventions on HIV incidence, suicide and CVD deaths in this population. Though the specifics of their inquiries differ, both articles conclude – perhaps unsurprisingly – that intervention strategies attending to both HIV and substance use could have substantial beneficial impacts on the comorbid conditions evaluated.

As with all models of complex systems, the models of Cepeda et al and Bórquez *et al*. require numerous input values to parameterize their many moving parts and make quantitative predictions under a range of hypothetical scenarios. Many of these inputs – such as the reduction in sexual HIV transmission afforded by adherent ART use – are relatively well-established after decades of concentrated study. Others, such as the effectiveness against HIV acquisition of interventions reducing stimulant use, are less certain. Fundamentally, the

inclusion of comorbid conditions and corresponding intervention types within HIV transmission modelling frameworks represents a relatively new frontier, requiring structural considerations, modelling assumptions and input values for which the requisite empirical evidence is still nascent.

FACING THE CHALLENGES AHEAD

The papers in this Supplement illustrate the potential value of modelling to inform policy relating to the integration of services for HIV and other conditions. But they also underscore the tremendous amount of work that still needs to be done in this area. Currently, very few data exist as to the effectiveness and costs of specific, scalable programmes that could effectively integrate HIV services and other health systems. Examples of data that could advance this field include: (a) implementation studies with embedded costing analyses of feasible integration programmes, from screening for diabetes and hypertension among PLHIV in care to integrated management of HIV and substance use for people who drink hazardously or use drugs; (b) pragmatic trials [19] of integrated versus stand-alone services, using patient-centred endpoints as outcomes to support the hypothesized causal link between effective integration and improved patient outcomes and (c) economic analyses – including collection of data on such processes as implementation, scale-up and economies of scale and scope – to test hypotheses about the estimated cost of integrated interventions from the provider perspective. Collection of such data in a range of epidemiological and economic settings could bolster the ability of models to project long-term impact and assess the cost-effectiveness of such interventions, thereby informing more effective policy and motivating the next generation of data-driven modelling.

In constructing such policy-relevant models, it is important to evaluate specific policies with attention to the underlying epidemiological context and existing health system, rather than expecting that conclusions or principles relevant to one setting will necessarily be generalizable to others. It follows that integrating HIV and other services may not be the best use of resources in some cases. While there is strong global momentum towards integrating health systems and providing UHC, there are likely many cases where integrating care may marginalize at-risk populations, produce regressive outcomes in terms of equitable sharing of health resources, or result in inefficient use of scarce healthcare resources that could be put to better use in other ways. Using models to investigate these unintended effects can help us more transparently and systematically consider the broader consequences – both positive and negative – of specific integration policies in specific settings.

As highlighted in the Viewpoint by Kupfer *et al.* [20], enhanced capacity in analysis and modelling is an essential step towards collection of relevant data and performance of effective analyses to inform in-country decisions regarding integration of HIV services with broader health systems. These authors highlight the importance of making analytic tools more broadly available, investing in training centres within low- and middle-income countries, and engaging directly with decision makers when constructing policy-facing analyses.

Finally, the papers in this Supplement highlight the importance of more precise thinking about integrated HIV services and their effects. "Integrated HIV care" is not a single intervention that can be universally applied; rather, this broad term encompasses a wide array of specific intervention and policy options that must be tailored to the appropriate population and evaluated individually. As data on such specific integrated HIV interventions emerge, models will evolve from the more generic approaches taken today to answering more specific research questions to help inform specific sets of decision makers. To be useful, this next generation of models will need to be more carefully calibrated to data for particular populations, more advanced in their ability to incorporate analyses of uncertainty and generalizability to other settings, and more grounded in empirical data about intervention effects (as those data emerge). They must also be more cognizant of potential secondary effects of HIV integration policy; such effects might include (a) adverse consequences to health systems and/or funding streams that are incapable of handling additional capacity and (b) unintended inequities from providing additional services to those who already have better access to other health services (while also acknowledging the potential efficiencies of doing so). The analyses presented in this Supplement are an important first step in the direction of informing HIV integration policy, but there is much more work to be done – in terms of collecting requisite data on effectiveness and costs of specific interventions as well as developing models that can exploit those data to their maximum utility.

In conclusion, this Supplement helps to define a path towards more evidence-based decision making in the context of integrating services for HIV and other conditions. It is currently hypothesized by many that such integration will lead to better health outcomes for patients and populations and more efficient use of resources. Coupled with collection of empirical data on the costs and effectiveness of specific interventions, models can help us to understand the contexts in which that hypothesis might be supported and those in which integration of HIV and other health services may not be such a priority. Better data and better models can help to define specific policy options and provide evidence as to which of those options should be advanced, and which should be reconsidered. Models are an important component of an evidence-based decision-making process for integrated HIV services, but current models also illustrate the urgent need to strengthen the research enterprise responsible for producing the data on which such models rely. In order to end the AIDS epidemic in the next decade while also achieving UHC, we must prioritize the collection of better data on integrated HIV services and the improvement of models themselves – and we must do so well before 2030 approaches.

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COMPETING INTERESTS

Dr. Dowdy is a co-author on the manuscript written by Kasaie *et al.* [11]. Dr. Powers has no competing interests to declare. Dr. Hallett was the recipient of a grant from Fogarty International that supported the work of one the papers in this Supplement.

AUTHORS' CONTRIBUTIONS

All authors served as Guest Editors to the Supplement and conceived the editorial. DWD wrote the first draft of the manuscript. All authors revised the manuscript for intellectual content and approved the final version submitted for publication.

ABBREVIATIONS

AIDS, acquired immune deficiency syndrome; ART, antiretroviral therapy; CVD, cardiovascular disease; HIV, human immunodeficiency virus; NCD, non-communicable disease; PLHIV, people living with HIV; PWID, people who inject drugs; UHC, universal health coverage.

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COMMENTARY

Recommendations for the use of mathematical modelling to support decision-making on integration of non-communicable diseases into HIV care

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Abstract

Introduction: Integrating services for non-communicable diseases (NCDs) into existing primary care platforms such as HIV programmes has been recommended as a way of strengthening health systems, reducing redundancies and leveraging existing systems to rapidly scale-up underdeveloped programmes. Mathematical modelling provides a powerful tool to address questions around priorities, optimization and implementation of such programmes. In this study, we examine the case for NCD-HIV integration, use Kenya as a case-study to highlight how modelling has supported wider policy formulation and decision-making in healthcare and to collate stakeholders' recommendations on use of models for NCD-HIV integration decision-making.

Discussion: Across Africa, NCDs are increasingly posing challenges for health systems, which historically focused on the care of acute and infectious conditions. Pilot programmes using integrated care services have generated advantages for both provider and user, been cost-effective, practical and achieve rapid coverage scale-up. The shared chronic nature of NCDs and HIV means that many operational approaches and infrastructure developed for HIV programmes apply to NCDs, suggesting this to be a cost-effective and sustainable policy option for countries with large HIV programmes and small, un-resourced NCD programmes. However, the vertical nature of current disease programmes, policy financing and operations operate as barriers to NCD-HIV integration. Modelling has successfully been used to inform health decision-making across a number of disease areas and in a number of ways. Examples from Kenya include (i) estimating current and future disease burden to set priorities for public health interventions, (ii) forecasting the requisite investments by government, (iii) comparing the impact of different integration approaches, (iv) performing cost-benefit analysis for integration and (v) evaluating health system capacity needs.

Conclusions: Modelling can and should play an integral part in the decision-making processes for health in general and NCD-HIV integration specifically. It is especially useful where little data is available. The successful use of modelling to inform decision-making will depend on several factors including policy makers' comfort with and understanding of models and their uncertainties, modellers understanding of national priorities, funding opportunities and building local modelling capacity to ensure sustainability.

Keywords: policy; integration; modelling; Kenya; non-communicable diseases; HIV

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1 | INTRODUCTION

The growing burden of non-communicable diseases (NCDs) in low- and middle-income countries calls for concerted efforts at prevention, early detection and optimization of health systems for effective chronic care delivery. Given the multi-morbid nature of NCDs [1,2], it also calls for a shift from fragmented health systems to more integrated and holistic care provision [3].

One of the approaches policy makers in countries with poorly resourced NCD programmes could consider is integration of chronic care services into existing robust primary health structures. An example of where this is taking place is Kenya, whose National Strategy for Prevention and Control of NCDs 2015 to 2020 emphasizes linkage of care between major NCDs and communicable diseases such as human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and tuberculosis (TB) [4]. Separate

care models can result in redundancies at the system, service and patient level, such as separate training programmes, laboratory infrastructure and data systems [5,6]. Integration is premised on the assumption that these redundant edges in well financed primary care platforms can be leveraged for under-resourced and under-developed programmes such as those for NCDs and that there exists potential for synergies and shared benefits for both provider and user in delivering integrated and comprehensive care packages.

However, many challenges and barriers to implementation of integrated service provision remain which necessitate evidence-based research to facilitate the translation of strategic and policy commitments to practical changes on the ground. Mathematical models have provided evidence-based guidance for decision-making around priorities, optimization and implementation of services. Although no modelling study has focused on the systematic evaluation of integration of NCD services into existing platforms, there are many examples from Kenya and the wider region of how mathematical models have supported decision-making more generally.

In this study, we examine the case for NCD-HIV integration, use Kenya as a case-study to highlight how modelling has supported wider policy formulation and decision-making in healthcare and to collate stakeholders' recommendations on use of models for NCD-HIV integration decision-making.

2 | DISCUSSION

2.1 | The burden of NCDs in sub-Saharan Africa

Across sub-Saharan Africa (SSA), NCDs are the second leading cause of morbidity and mortality after HIV/AIDS [7], yet global financing for NCDs comprises less than 2% of total health expenditure [8]. Studies from both high income countries and LMICs have shown that people living with HIV (PLHIV) experience a higher NCD burden [2,9,10]. A recent modelling study estimates that 51% of Kenyan adults currently suffer from ≥1 NCD, that this burden was higher in PLHIV compared to HIV negative and is projected to increase [11]. It identified hypertension, elevated total cholesterol, diabetes, chronic kidney disease and depression as the most prevalent NCDs, with cardiovascular disease and cancer as the main NCD-related causes of deaths, irrespective of HIV status [11]. While the mechanisms of NCDs in the context of HIV are not fully understood, they likely involve complex interactions between traditional risk factors, including smoking, diet, and exercise, and HIV-specific risk factors, including long-term immune activation, inflammation and toxicity related to long-term ART use [2].

Every country in the region will have outlined their priorities for NCDs in their national strategic plan. In Kenya, the National Strategy for Prevention and Control of NCDs 2015 to 2020 lays emphasis on four major NCDs: cardiovascular conditions, cancers, diabetes, and chronic obstructive pulmonary diseases and their shared risk factors [4]. The Kenyan Poverty Commission found that NCDs decrease household income by an estimated 29% and can subject families to catastrophic expenditures and poverty [12]. This threatens the achievement of Universal Health Coverage (UHC) aspired by the region, as one of the pillars of UHC is to cushion individuals, households and communities from catastrophic and impoverishing health expenditures [13].

2.2 | The case for integrated care

Integration of health services is the foundation of primary healthcare and will form the foundation of UHC [14]. Integration has been shown to generate advantages for both provider and user, and has been demonstrated to be cost-effective, practical and rapidly scalable [15-17]. For the users, integration can increase equity, decrease stigma associated with healthcare demand, improve access to services and disease outcomes [18]. For example, The Integrated Management of Childhood Illness initiative uses a comprehensive primary care-based service delivery model to reduce both morbidity and mortality and promote improved health childhood development [19]. From the supply side, integration can generate economies of scope and reduce redundancies in resource limited settings [14]. For example, leveraging existing infrastructure such as buildings, laboratory and supply chains can generate economic savings while joint supervision, training and mentorship has been shown to reduce demand on health workers' time [14].

2.3 | Forms of integration

Integration may take various forms [14,20], with many approaches already successfully operating in SSA. In Kenya, integration to date is mainly in the areas of infectious disease and maternal and child health. Integration can focus on providing a package of preventive and curative health interventions for a particular population group, such as the "Integrated Management of Childhood Illnesses" programme. Similarly, integration can involve offering multiple services for diseases requiring common interventions under "one roof," such as integrating nutritional services in Diabetes Centers of Excellence which include integration of laboratory and supply chains. Finally, integration at the policy level can include jointly agreed health sector strategies, joint health sector performance reviews and sector-wide approaches.

2.4 | HIV as an example of integrated care

The HIV response provides, perhaps, the best example of how integration can be successfully operationalized for chronic conditions. Despite being an infectious disease, care for HIV has evolved into a chronic care model, that involves patient follow-up, continuity of care, monitoring and auxiliary services to maintain patients' health and quality of life. HIV/AIDS prevention and treatment services have been successfully integrated with services focused on maternal and child health, TB, nutritional advice, family planning services, lifestyle advice services and screening programmes for NCDs [21-23], and has established strong health systems, financing and infrastructure across many LMIC settings.

2.5 | The case for NCD-HIV integration

It is clear, given the large and growing burden of NCDs in both PLHIV and the general population across SSA, that services for the screening and treatment of NCDs will play an

important role in the preservation of health. Building on HIV platforms could shorten the learning curve for NCD prevention and control [24-27], particularly for countries with large HIV programmes and small, un-resourced NCD programmes. Considering their shared chronic nature, a majority of the programmatic and operational approaches and infrastructure developed for HIV programmes could be used for NCDs, especially in resource-constrained settings [18]. For instance, the surveillance systems that have been used in the HIV response can be leveraged to quantify the magnitude of NCDs, the cost of prevention and management, identify vulnerable population groups and assess the effects of policy and operational interventions [24]. Other potential areas of integration for NCDs include peer support, m-Health and community-based screening [17]. In fact in Uganda leveraging the HIV prevention and care infrastructure to deliver multi-disease services (hypertension and diabetes) resulted in marginal incremental cost of integrating screening for these NCDs compared with the cost of HIV testing [28].

Despite the numerous merits of NCD-HIV integration, concerns remain, including that integration may compromise existing successes and reverse HIV advances that have been achieved. There are concerns around (i) inequity in NCD care provision in early phases of implementation, with more NCD care for PLHIV than the general population, (ii) how service provision designed for low-prevalence diseases could be scaled up rapidly enough to deal with highly prevalence NCDs such as hypertension and (iii) how individual and environmental barriers to NCD care seeking behaviour can be overcome [29]. Other challenges to providing fully funded programmes at no or low cost to patients include the need for significant upfront investments, provider training and set up of robust supply chains. This is further compounded by the exclusivity that characterizes current vertical disease programming, policy, financing and operations. Finally, NCDs are complex and attract low financing, while an expectation of free services and medications was created by HIV care.

In this era of UHC and with the push towards more domestic financing, the potential benefits seem to outweigh the risks of integration, however, by providing opportunities to strengthen the health system at large. Nevertheless, each disease entity within NCDs has its unique challenges, and these should be considered when planning for integration. As Kenya and other countries around the region focus on rolling-out integrated NCD-HIV programmes, they will need to be guided by robust evidence around priorities, optimization and implementation of these programmes in order to both ensure return on investment and safe-guarding of existing programmes.

2.6 | Why mathematical modelling?

Mathematical modelling provides a powerful synthesizing tool, with multiple applications in the health sector and policy development. Although to date no modelling study has focused on systematic evaluation of integration of NCD services into existing platforms, there are many examples of how mathematical models have supported decision-making, particularly in the field of infectious diseases and HIV. In this section, we use Kenya as a case-study to highlight how modelling has supported wider policy formulation and decision-making in healthcare and later collate stakeholders' recommendations on use of models for NCD-HIV integration decision-making. While we focus on Kenya as a case study, the lessons, priorities and recommendations identified will apply to other LMICs with large HIV and un-resources NCD programmes and to the use of modelling in decision-making more widely.

2.7 | The role of mathematical models in estimating disease burden

Estimates of disease burden, as well as projections of how these may change over time are crucial to inform strategic planning of health services in the country, yet surveillance systems in many LMIC countries still focus on capturing data on only a handful of key areas, such as infectious diseases, child and maternal health and death registries. Accurate NCD data for policy utility has been a major bottleneck in all SSA due to the lack of surveillance systems for these diseases. Data on NCDs in many countries, including Kenya largely derived from the WHO Stepwise Survey [30] or geographically limited, usually pilot, research studies. Kenya is in the process of strengthening NCD indicators in the national health information systems to provide routine reliable data to inform planning. To bridge the current data gap, mathematical modelling utilizing multiple data sources to extrapolate NCD outcomes provides an opportunity to improve the availability and accuracy of locally relevant data for policy and programming.

There are many examples of how mathematical models have been used to establish the burden of individual infectious diseases and generate risk maps, for example HIV, TB and malaria at national or sub-national levels across SSA [31-34] and have long been used to generate annual HIV estimates that aid in planning and resource mobilization in Kenya. However, few models have establish the burden of multimorbidity of NCDs [11,35-38]. In 2019, modelling was used to provide the first-ever national estimates of six NCDs and eight cancers by HIV status in Kenya, by combining a data landscaping exercise of available NCD data, and triangulating it with demographic data in a modelling framework [11]. The results will be summarized in the first ever national report on NCD estimates in 2020 and will help inform priorities around integrated NCD-HIV activities.

2.8 | The role of modelling in optimizing healthcare provision

Within the realms of health system optimization, models have been used to identify health care priorities, including systematic comparison of prevention measures, and evaluations of the cost-effectiveness of integrating health services [39-43]. Many of these findings have fed directly into national and global policy. For example, the 2014/2015 to 2018/2019 Kenya AIDS Strategic framework includes recommendations informed by a modelling exercise [40,44]. This model analysis found that selectively targeting primary HIV prevention interventions to population and regions at highest risk of HIV could achieve a 55% reduction in new HIV cases by 2030, compared to 40% when interventions were adopted uniformly across the country [40]. More recently, the World Health Organization launched its global strategy for cervical cancer

Table 1. Summary of priority research questions on the pathway to integration as collated through consultation with key stakeholders

1. What is the impact of integration on improving access to primary prevention services?
2. What is the optimal entry-points for integration (e.g. HIV platforms, child health to deliver health services to siblings and mothers)?
3. What risk does integration pose at jeopardizing the gains made in the primary platform, for example, HIV programme?
4. Are there economies of scope relating to integration of individual services?
5. How does regional disease prevalence affect the cost-effectiveness of integration?
6. What is the impact of reducing or removing user fees on cost-effectiveness of integration/what are the optimal user fees contribute for services under UHC?
7. Within which laboratory sample transport system should NCD diagnostic samples be integrated?
8. What components have the greatest impact when integrated along the continuum of care and what are the markers of success?

HIV, human immunodeficiency virus; NCDs, Non-communicable diseases; UHC, Universal Health Coverage.

elimination, which was informed by an extensive modelling consultation [41].

2.9 | The role of mathematical modelling in exploring health system capacity needs

Finally, models have also been used to explore questions around task-shifting, human resources needs, and optimization of health financing mechanisms [45-48]. In Kenya, one study looked at long-term economic impact of return on investment and found that shifting cognitive behavioural therapy to reduce alcohol abuse among PLHIV to paraprofessionals is effective and economical and averts alcohol-related morbidity and mortality [45]. Another study evaluated optimal financial mechanisms to sustain UHC in Kenya, including social health insurance and general tax-funding mechanisms [46]. The study provided recommendations for long-term financial sustainability, which included a tax-funding system and innovative financing options [46].

2.10 | Recommendations for the use of mathematical modelling to support NCD-HIV integration

NCD-HIV integration appears to be a cost-effective and sustainable policy option for countries with large HIV programmes and small, un-resourced NCD programmes to rapidly scale-up their NCD programmes, and has been fully adopted by the Kenya's National Strategy for Prevention and Control of NCDs 2015 to 2020 [4]. Yet several key policy level research gaps for NCD-HIV integration remain to be addressed, to ensure these programmes are successful. Modelling has proven to be a powerful tool to support decision-making. We carried out stakeholder consultation and collation of targeted expert opinions. This was done in a snow balling activity between June and September 2019, and included modellers from several international institutions who have supported evidence generation for policy, funders who have worked on the interface between research and policy and policy makers in Kenya from across the Divisions of Cancers, NCDs, HIV and the strategic team at the Ministry of Health. The focus of this consultation was to (i) define key questions around NCD-HIV integration, (ii) identify where and how to integrate modelling within the policy making process, (iii) identify pre-requisites for the successful use of models in policy formulation and decision-making.

The consultation highlighted eight key priority research question questions from national stakeholders, which can be addressed by modelling (Table 1). Within the well-defined steps of policy and decision making for health, we suggest that modelling methodology is likely to provide a critical entry point for enhancing these integration efforts in various ways. Policy formulation is driven by the need to provide alternative strategies or guidance for a given gap in health provision and is supported by a formal evaluation process (Figure 1). Modelling can be an important tool in the evaluation process, particularly in areas were little data exist or data collection is weak or unfeasible (Figure 1). The consultation highlighted that the use of modelling for policy formulation and decision making should be accompanied by defined processes, including formal integration into the decision-making process, robust technical review and dissemination (Figure 1 and Table 1).

Several prerequisites are were identified through the consultation, for modelling to drive the integration agenda in a sustainable manner (Table 2). First, it emphasized that in order to successfully use modelling to support decision-making, the application of the models will need to be aligned with the current national aspiration and their use will need to gain wider acceptance as well as the backing of policy makers. Second, policymakers need to be sensitized on the role of modelling in public health, its approaches and techniques, assumptions and limitations. A strong and honest collaboration between modellers and policy makers is crucial to harness the potential for modelling in enhancing the integration agenda. Third, results from models should be widely disseminated, processes evaluated and validated. Models should, as with laboratory experiments, be sufficiently transparent that their results can be replicated. Fourth, models should be linked to existing surveillance and national health information systems, to ensure models serve a complementing, not a duplicating or replacing function. A case example in Kenya is in HIV surveillance system, whereby routine reporting and periodic surveys is combined with modelling to provide up-to-date information continuously.

Finally, application of modelling in public health planning and policy formulation must be conducted in a sustainable manner and include human resource capacity for modelling. Several approaches can be utilized for this purpose: availing of resources to institutionalize, maintain and sustain mathematical models to enhance visibility on their role, foster

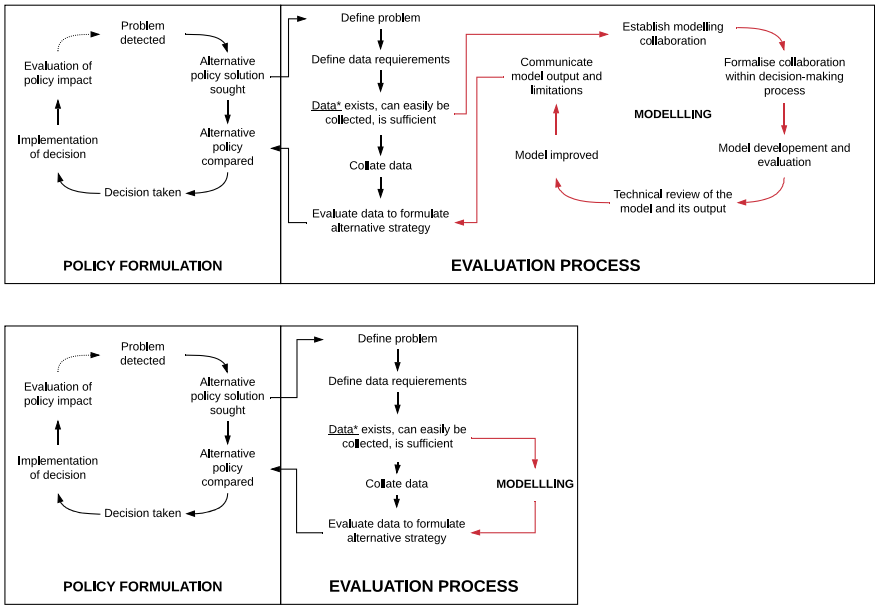

Figure 1. The role of mathematical modelling to inform policy decisions on integrated care for multi-morbidity in Kenya. *Data referring to primary or programmatic data and expert opinions.

collaboration among institutions that routinely utilize modelling to enhance partnerships and knowledge transfer and incorporating modelling in local public health training to increase the skill pool and create a critical mass of modellers. A critical bottleneck remains the sustainability of these efforts. Modelling to inform policy frequently involves collaborations between academic institutions, which generally house modelling capacity, and governmental organizations. Academic groups rely on funding through outside sources, with funding schemes often being project specific and time limited. Altogether this means that collaborations between modellers and governments can suffer from a lack of sustainable funding. Additional funding focused on support for capacity building of in-country modellers and support for the transfer of models to countries will help ensure sustainability and continuity of efforts.

Table 2. Key stakeholder recommendations to formally and sustainably integrate modelling in policy formulation and decision-making

1. Align modelling with current national priorities
2. Sensitize policy makers to the role of modelling in policy formulation and decision-making
3. Ensure wider acceptance as well as the backing of policy makers for modelling
4. Develop a set of guidelines to evaluate the transparency, robustness and replicability of models
5. Develop a formal review of model design and output by a national technical team trained in modelling
6. Disseminate results from any policy/modelling exercise and highlight the model's limitations
7. Link models to the formal national health information systems to avoid duplication and increase efficiencies
8. Foster collaboration with established institutions that routinely utilize models to ensure knowledge transfer
9. Incorporate modelling in public health training in local institutions to build modelling capacity
10. Identify national resources to support sustainability and institutionalization of mathematical modelling

3 | CONCLUSIONS

It seems clear that mathematical modelling can and should play a central role in future policy formulation and decision-making as the sub-Saharan region grapples with questions of integration and focuses on rolling out UHC, particularly given the often limited evidenced-based data to support decisions. Models have played a central role in informing policy in other disease areas, demonstrating that they can provide a strong platform of credible research. They will undoubtably be able to generate valuable and robust evidence to answer some key questions that remain regarding NCD-HIV integration in the region (Table 1).

First, by estimating burden, modelling can support decision-makers in setting priorities for public health policy interventions. This is key for health conditions with inadequate or weak surveillance systems and therefore little data for decision-making, of which NCDs are a good example. Second, if policy formulation or revision is required, modelling can be utilized for the formulation of optimized options for an integration approach, cost-benefit analysis for integration as well as evaluating the impact of integration of services. Finally, models can be utilized in conducting projections of future

trends of various health conditions and aid in forecasting the requisite government investments to address them effectively. This is particularly vital for SSA as the triple burden of disease phenomenon manifests in the setting of dwindling donor support. For instance, with integration, there is likely to be increased workload for human resources, and the need for additional equipment and commodities and/or. Thorough forecasting will forestall shortages of commodities and/or waste of resources as the models may provide indicative trends.

Integration of health services will require a policy backing for wide acceptability and sustainability beyond specific programmes. In addition, the change in the system of service delivery towards integration will require the interplay of political, technical and administrative action at several levels, including sustained commitment from the government, and the bridging of critical knowledge gaps. Within the well-defined steps of policymaking for health, we suggest that modelling methodology is likely to provide a critical entry point for enhancing these integration efforts (Figure 1).

Both integration and modelling ought to be aligned with the current national health priorities to gain wide acceptance and backing. A good example is putting all these efforts in the context of expansion of primary healthcare and national rollout of UHC. While encouraging the use of mathematical models, it is critical to emphasize that they are not a replacement of empirical data collection but rather a tool to assist in interpretation of this data to a more useful form.

Successful use of modelling to inform policy and decision-making will depend on several factors (Table 2) including policy makers' comfort with and understanding of models and their uncertainties, modellers understanding the policy questions, funding opportunities and building local modelling capacity to ensure sustainability. While we focus on Kenya and NCD-HIV integration as a case in point, recommendations also apply to other settings and the use of modelling in policy formulation and decision-making more widely.

It is clear that modelling has played a valuable role in the formulation of policy recommendations and decision-making across a number of disease areas and in a number of settings to date. As the paucity of NCD data for policy use in Kenya and the wider region continues to hamper policy decisions on integration, mathematical modelling should play an integral part in bridging this gap now and in the future. This paper outlines a set of clear recommendations on how to sustainability integrate modelling into decision making.

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COMPETING INTERESTS

All authors report no conflicts of interest.

AUTHORS' CONTRIBUTIONS

MS, JK and LK conceived the paper, formulated the overall aim, scope and lens of the manuscript, with all authors contributing to finalizing its outline and scope. MS, VM, JK, OO and PNPG wrote the first draft of the manuscript. MS, JK, VM, OO, BB, BW, LK and PKS led the design and development of all infographics. JK, VM, OO, JHK, MKK and NK led all aspects of the policy landscape and research gaps in Kenya. MS, PNPG, BW and PKS led all model-related aspects of the manuscript. All authors contributed to the re-drafting of the manuscript and in the process of approving the final draft.

ABBREVIATIONS

AIDS, Acquired Immune Deficiency Syndrome; HIV, Human Immunodeficiency virus; NCDs, Non-communicable diseases; PLHIV, People Living with HIV; SSA, Sub-Saharan Africa; TB, tuberculosis; UHC, Universal Health Coverage.

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COMMENTARY

Integrating care for non-communicable diseases into routine HIV services: key considerations for policy design in sub-Saharan Africa

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Abstract

Introduction: There is great interest for integrating care for non-communicable diseases (NCDs) into routine HIV services in sub-Saharan Africa (SSA) due to the steady rise of the number of people who are ageing with HIV. Suggested health system approaches for intervening on these comorbidities have mostly been normative, with little actionable guidance on implementation, and on the practical, economic and ethical considerations of favouring people living with HIV (PLHIV) versus targeting the general population. We summarize opportunities and challenges related to leveraging HIV treatment platforms to address NCDs among PLHIV. We emphasize key considerations that can guide integrated care in SSA and point to possible interventions for implementation.

Discussion: Integrating care offers an opportunity for effective delivery of NCD services to PLHIV, but may be viewed to unfairly ignore the larger number of NCD cases in the general population. Integration can also help maintain the substantial health and economic benefits that have been achieved by the global HIV/AIDS response. Implementing interventions for integrated care will require assessing the prevalence of common NCDs among PLHIV, which can be achieved via increased screening during routine HIV care. Successful integration will also necessitate earmarking funds for NCD interventions in national budgets.

Conclusions: An expanded agenda for addressing HIV-NCD comorbidities in SSA may require adding selected NCDs to conditions that are routinely monitored in PLHIV. Attention should be given to mitigating potential tradeoffs in the quality of HIV services that may result from the extra responsibilities borne by HIV health workers. Integrated care will more likely be effective in the context of concurrent health system reforms that address NCDs in the general population, and with synergies with other HIV investments that have been used to strengthen health systems.

Keywords: HIV/AIDS; non-communicable diseases; antiretroviral therapy; integrated care; sub-Saharan Africa

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1 | INTRODUCTION

The global response to the HIV epidemic in sub-Saharan Africa (SSA) has resulted in large declines in HIV-related deaths, and contributed to substantial increments in life expectancy [1]. Despite this progress, new adult infections remain high in the region with over 900,000 new cases reported in 2018 [2]. Additionally, for many countries, the epidemic is becoming more concentrated in middle-age groups that also have a large proportion of individuals who are at high risk for non-communicable diseases (NCDs) [3]. For example, in Uganda, although the prevalence of HIV had reduced to 6% by 2017, 14% of men and 11% of women aged 45 to 49 years were HIV positive [4].

With the rapidly increasing number of people who are ageing with HIV and the resulting steady rise of NCDs in this population [5], there has been growing enthusiasm and advocacy for integrating care for NCDs into routine HIV treatment services in SSA [6]. In spite of a similar increase in the prevalence of NCDs in the general population, interventions for NCDs are rarely included in national primary care packages and are often paid for via out-of-pocket medical payments, which can lead to "catastrophic" expenditure and medical impoverishment [7]. Also, the global AIDS response that is primarily donor-supported has been set up to address HIV and common opportunistic infections, with limited focus on other conditions [8]. This has resulted in significant gaps in the cascade of care for NCDs in countries that are on track to meeting the aspirational 90-90-90 targets [9].

In SSA, integration of care for other conditions with HIV services at a national level has perhaps been best demonstrated for prevention of mother-to-child transmission of HIV

with 85% coverage achieved [10]. Capitalizing on the remarkable achievements and lessons learnt from the HIV/AIDS response, integrating services for HIV and NCDs could enable the delivery of appropriate, and affordable healthcare to millions in need [11]. The narrative on integrated care for HIV and NCDs in SSA has mostly emerged from the perspective of improving access to interventions for NCD services for people living with HIV (PLHIV) [6,11]. Less attention has been devoted to the in-depth examination of the practical, economical and ethical considerations of prioritizing PLHIV as opposed to targeting the general population that is also experiencing a rapidly growing prevalence of NCDs. Furthermore, suggested health system approaches for addressing HIV-NCD comorbidities have mostly been normative, and have provided little actionable guidance on how to implement specific interventions, especially in SSA [12,13]. We summarize key opportunities and challenges for using HIV treatment platforms to address NCDs among PLHIV. We emphasize essential considerations that can guide integrated care in SSA and point to possible interventions for implementation.

2 | DISCUSSION

The increasing rates of HIV-NCD comorbidities present significant challenges to health systems in many low- and middle-income countries (LMICs), that are technically and financially constrained, and have mostly been designed to respond to communicable, maternal and childhood conditions. Policymakers in these countries are now faced with a decision on whether to favour interventions for integrating NCD care and treatment into existing HIV services, as opposed to embarking on broader health system reforms for addressing NCDs in the general population. There are substantially more NCD cases among HIV-negative individuals essentially because of their larger proportion within the total population when compared to PLHIV. Proponents of broader reforms may support the principle of using a "veil of ignorance" and thereby not considering individuals' characteristics (in this case HIV-NCD comorbidities) when allocating scarce resources [14]. Focusing on the general population is also a more equitable option, but would inevitably be costlier and more difficult to implement. In contrast, an approach that favours integrating care for NCDs with existing HIV services would potentially be easier and more affordable to implement because of the regular visits that PLHIV make to health facilities. The already existing counselling and laboratory services, skilled human resources and drug supply chain mechanisms of ART delivery could be expanded and utilized to deliver high-quality services for NCD care to PLHIV with more manageable added costs. Integrating HIV and NCD care could also potentially lead to economies of scale (i.e. decrease in costs as programmes expand in volume) and economies of scope (i.e. decrease in costs as programmes jointly provide multiple services onto the same delivery platform), and thus improve efficiency, patient outcomes and enhanced responsiveness to local needs [15]. Choosing to first address NCDs in PLHIV might however be seen as unfair, as it would ignore the larger number of NCD cases in the general population [16].

We propose that countries embark on gradual integration of NCD care into existing HIV services, and view this as a means of providing the necessary comprehensive care to people who are ageing with comorbidities. We acknowledge that this approach may increase the current disparities in access to healthcare between PLHIV and the general population. Yet, inaction could otherwise jeopardize the substantial health and economic benefits that have been achieved while scaling up ART services. We further propose that this integration be implemented concurrently with broader health system reforms that address NCDs in the general population, which would in part help mitigate the inequalities created by prioritizing PLHIV.

A second key consideration for integrated care is identifying specific conditions to prioritize in HIV treatment programmes. The extensive literature documenting the increasing rates of HIV-NCD comorbidities is mostly from subnational studies that have reported on conditions like obesity and hypertension [17-21]. Some studies have also provided pooled estimates on the prevalence of these comorbidities in LMICs [5]. However, country-specific estimates on the prevalence of common NCDs in PLHIV remain largely unknown for most of SSA. HIV treatment programmes generally do not track NCD comorbidities essentially because there are no associated reporting requirements for these conditions. Most countries also do not have national surveys that jointly collect data on HIV status and NCDs. The World Health Organization-supported STEPS surveys on NCD risk factors that are available in many LMICs do not collect information on HIV status [22]. Likewise, the Population-based HIV Impact Assessments that are now widely used for estimating HIV prevalence in SSA only focus on HIV [3]. Indeed, more granular information on the prevalence of HIV-NCD comorbidities would be required to determine the cost of integrated care and set priorities. For example, it was recently modelled that in Uganda it might be more cost-effective to target older PLHIV (45 years or older) for routine screening for hypertension, diabetes and dyslipidemias because of the higher prevalence of the three conditions at these ages [23].

To address some of the current information gaps, we propose that HIV treatment programmes prioritize routine screening of NCDs that are commonly seen in PLHIV (Box 1). These conditions can also be added to the set of indicators that are routinely monitored by ART delivery programmes. Specific attention could be given to regular body weight assessments because of the increasing rates of excessive weight gain among patients on ART (Table 1) [19,21,24]. Excessive weight gain is concerning because a high body mass index (BMI) is a major risk factor for several NCDs and has been linked to increased risk for all-cause mortality [25]. Body weight assessments are already part of routine HIV care but current guidance mostly focuses on weight gain as a positive sign of immune recovery. Emphasis can also be put on improving the capacity of health facilities to measure height and on periodic interpretation of BMI values. Similarly, more routine blood pressure assessments could be undertaken because of the observed high rates of hypertension in PLHIV [19,21]. Enhanced blood pressure screening would also help address the gaps in the cascade of care for hypertension that have been observed in HIV treatment programmes with high levels of virologic suppression [9].

These suggested intensified screening procedures would be implemented while taking into consideration the possibility of further straining an already burdened health system. Although

Box 1. Policy implications

We recommend the following to be considered in addressing the growing prevalence of NCDs in people who are ageing with HIV in sub-Saharan Africa.

- There is an urgent need for expanding the global agenda for combating the HIV epidemic to include care for common NCDs in PLHIV, so to sustain the substantial health and economic benefits that have been achieved with scaling up ART services.
- Integrating NCD care into existing HIV services should be viewed as a means of providing the necessary comprehensive care to PLHIV ageing with comorbidities.
- Broader health system reforms to address NCDs in the general population will be essential to improve access to services for conditions that might not be adequately managed in HIV treatment settings.
- Prevalence and incidence of common NCDs in PLHIV can be included in the set of indicators that are routinely monitored by ART delivery programmes.

Table 1. Non-communicable disease risk factors and conditions for consideration for screening among people living with HIV in sub-Saharan Africa

Risk factor/disease	Prevalence (95% CI)	Proposed intervention
Smoking	Men: 25.9% (24.6 to 27.3) Women: 1.2% (0.9 to 1.4) [32]	Increase screening and counselling on smoking and tobacco use
Weight gain and obesity	27.3% (20.2 to 35.9) [5]	Implement recommended body weight monitoring in routine HIV care Carry out periodic tracking of proportion of overweight or obese PLHIV in HIV treatment programmes
Hypertension	21.2% (16.3 to 27.1) [5]	Increase blood pressure monitoring in routine HIV care Carry out periodic tracking of proportion of hypertensive PLHIV in HIV treatment programmes
Hypercholesterolemia	22.2% (14.7 to 32.1) [5]	Prioritize determining the prevalence of dyslipidemias in PLHIV to identify high-risk age groups
Diabetes mellitus	1.3 to 18.0%[a] [5]	Prioritize determining the prevalence of diabetes mellitus in PLHIV to identify high-risk age-groups

BMI, body mass index; PLHIV, People living with HIV.
[a]Estimates only available as a range.

integrated care can lead to better patient outcomes [15], additional responsibilities on health workers could compromise the quality of existing HIV services. As a first step, changes in current practice can be limited to a few services, and preferably those that are already part of recommended care and use existing infrastructure. For example, although HIV programmes can be used for cervical cancer screening and management, the feasibility of such a programme might be compromised by the high costs incurred [26]. Cervical cancer programmes may therefore be more attainable as part of a nationwide strategy targeting the general population.

At the national level, periodic surveys could be designed to collect information on both HIV/ART status and common NCDs and their risk factors. The STEPS surveys could be modified to collect information on HIV status. This modification would also provide required estimates on the prevalence of conditions that are difficult to assess in routine HIV care, such as diabetes and dyslipidaemias.

Lastly, successful implementation of integrated care will require mobilizing additional funds to expand HIV treatment programmes to intensified screening and management of NCDs. In spite of the increasing prevalence of NCDs in SSA, current funding for NCD interventions mostly comes from domestic sources and has been shown to be inadequate [27,28]. Many countries now have strategic plans for addressing NCDs but implementation of the identified interventions has been limited by severe financial constraints [29]. In addition, although medications for common NCDs are now included in most national Essential Medicines Lists, frequent stockouts and inadequate management of drug supply chains repeatedly occur at health facilities in the public sector [30]. These funding and health system constraints have contributed to gaps in access to NCD services for PLHIV [9]. Similar gaps have been documented in the general population which has fewer encounters (compared with PLHIV) with the health system [31].

Addressing these substantial financing challenges will necessitate mobilizing additional funds for delivering high-yield NCD services to PLHIV and the general population. As global agencies recognize the risks posed by the rise of NCDs among ageing PLHIV, there is a need for coordinated efforts to address HIV-NCD comorbidities. However, given that

global funding for HIV/AIDS programmes has plateaued in recent years [11], the interventions that we propose for consideration are more likely to succeed in the context of increased budgetary allocation to NCDs by ministries of health in the short term. Increased domestic allocations may also in part reduce the inequalities that would be created by interventions that would only target PLHIV. There is also a need for more research on how to capitalize on the remarkable achievements of the HIV/AIDS response to deliver high-yield services to the general population.

3 | CONCLUSIONS

An expanded agenda for addressing common NCDs in PLHIV can help maintain the substantial health and economic benefits that have been achieved by the HIV/AIDS response.

Integrated care for NCDs in HIV treatment settings will require country-specific estimates on the proportion of PLHIV who need access to NCD services. Successful integration will also require earmarking additional funding for delivering high-yield NCD services for PLHIV. Attention should be given to mitigating potential tradeoffs in the quality of HIV services that may result from the extra responsibilities borne by HIV health workers, and to evaluating ways of scaling up successful interventions in HIV treatment settings to the general population.

Although integrated care can increase access to necessary services, the interventions we suggest are more likely to be effective in the context of gradual health system reforms for addressing NCDs in the general population. Investments in broader reforms will be essential to improve access to services for conditions that might not be adequately provided for in HIV treatment settings, such as cancer screening and treatment, as well as long-term care of mental health disorders in PLHIV. Advancing care for these conditions will require improvements in patient referral mechanisms, better use of Health Management Information Systems, and increasing access to specialized services. Likewise, synergies with other existing health investments should be prioritized, such as the HIV investments that have been used to strengthen health systems.

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COMPETING INTEREST

We declare no competing interests.

AUTHORS' CONTRIBUTIONS

AK conceived the policy suggestions that are discussed in this commentary in consultation with all co-authors. AK wrote the first draft of the manuscript, under supervision of SV. DS, DG, SO, GM, NAM and GD provided advice on the content of the manuscript. All authors contributed to writing and reviewing the manuscript.

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RESEARCH ARTICLE

Integrated screening and treatment services for HIV, hypertension and diabetes in Kenya: assessing the epidemiological impact and cost-effectiveness from a national and regional perspective

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Abstract

Introduction: As people with HIV age, prevention and management of other communicable and non-communicable diseases (NCDs) will become increasingly important. Integration of screening and treatment for HIV and NCDs is a promising approach for addressing the dual burden of these diseases. The aim of this study was to assess the epidemiological impact and cost-effectiveness of a community-wide integrated programme for screening and treatment of HIV, hypertension and diabetes in Kenya.

Methods: Coupling a microsimulation of cardiovascular diseases (CVDs) with a population-based model of HIV dynamics (the Spectrum), we created a hybrid HIV/CVD model. Interventions were modelled from year 2019 (baseline) to 2023, and population was followed to 2033. Analyses were carried at a national level and for three selected regions (Nairobi, Coast and Central).

Results: At a national level, the model projected 7.62 million individuals living with untreated hypertension, 692,000 with untreated diabetes and 592,000 individuals in need of ART in year 2018. Improving ART coverage from 68% at baseline to 88% in 2033 reduced HIV incidence by an estimated 64%. Providing NCD treatment to 50% of diagnosed cases from 2019 to 2023 and maintaining them on treatment afterwards could avert 116,000 CVD events and 43,600 CVD deaths in Kenya over the next 15 years. At a regional level, the estimated impact of expanded HIV services was highest in Nairobi region (averting 42,100 HIV infections compared to baseline) while Central region experienced the highest impact of expanded NCD treatment (with a reduction of 22,200 CVD events). The integrated HIV/NCD intervention could avert 7.76 million disability-adjusted-life-years (DALYs) over 15 years at an estimated cost of $6.68 billion ($445.27 million per year), or $860.30 per DALY averted. At a cost-effectiveness threshold of $2,010 per DALY averted, the probability of cost-effectiveness was 0.92, ranging from 0.71 in Central to 0.92 in Nairobi region.

Conclusions: Integrated screening and treatment of HIV and NCDs can be a cost-effective and impactful approach to save lives of people with HIV in Kenya, although important variation exists at the regional level. Containing the substantial costs required for scale-up will be critical for management of HIV and NCDs on a national scale.

Keywords: HIV; diabetes mellitus; hypertension; Kenya; cost-benefit analysis; computer simulation

Additional Supporting Information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

The HIV epidemic in Kenya is one of the largest globally, with an estimated 1.6 million people living with HIV (PLHIV) in 2018 [1]. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), approximately 89% of PLHIV knew their status and 75% were on treatment in 2018 [2], leaving a gap in HIV testing and treatment initiation. At the same time, the burden of non-communicable diseases (NCDs) in Kenya is increasing. Data from a Kenya health and demographic surveillance system found that deaths due to NCDs increased from 35% of total deaths in 2003 to 45% in 2010 [3,4]. The 2015 Kenya STEPwise approach to Surveillance (STEPS) survey reports the age-standardized prevalence of hypertension at 24.5%, pre-diabetes at 3.1%, and diabetes mellitus at 2.4% [4]. Importantly, only 15.6% of those with hypertension were aware of their elevated blood pressure, and among those aware, only 26.9% were on treatment [4]. For those with pre-diabetes or diabetes mellitus, 43.7% were aware of their condition and about 20% were on treatment [4].

In response to the ongoing epidemic of HIV and increasing burden of NCDs, and realistic restrictions in health budget, policy makers require efficient approaches to resource allocation. One such approach is the community-based, multi-disease testing and treatment strategy used in the Sustainable East Africa Research in Community Health trial, or SEARCH [5]. This trial, based in rural Uganda and Kenya, provided integrated screening for HIV, hypertension and diabetes, and facilitated linkage to care for those in need of treatment [5]. The results suggest the intervention's success in achieving high levels of testing coverage, linkage to HIV and NCD care and viral suppression after 1-year [6-8]. Nevertheless, the population-level impact and cost-effectiveness of such interventions at a national level remain uncertain. Furthermore, regional heterogeneities in factors relating to HIV transmission, NCD burden and population demographics may result in differential effectiveness and efficiency of such programmes when implemented at a regional level. As such, we sought to model the epidemiological impact and cost-effectiveness of an integrated programme similar to project SEARCH at a national and regional level in Kenya.

2 | METHODS

Coupling a microsimulation of cardiovascular diseases (CVDs) with a population-based HIV model (the Spectrum [9]), we created a hybrid model of HIV/CVDs (Figure 1). Population demographics and HIV epidemiology were estimated from Spectrum, and individual-level risks for NCDs were estimated from the 2015 Kenyan STEPwise survey [10]. Separate models were developed to represent Kenya at a national level and for three selected regions (namely Nairobi, Central and Coast). Access to all data and models were granted through corresponding agencies. Patient consent and ethical review were not required.

2.1 | The Spectrum model

The Spectrum software (Avenir Health, Glastonbury, CT, USA) is applied by the Joint United Nations Programme on HIV/AIDS (UNAIDS) to estimate key HIV indicators for 161 countries around the world [9]. Country-specific models are maintained and updated by a team of country expert on a regular basis. The Kenyan AIDS impact model (AIM) is calibrated to the 2019 official HIV estimates from National AIDS Control Council. Access to the latest release of national and regional Spectrum models was granted through UNAIDS (Data S1). This deterministic model represents a simplified representation of HIV and demographics in Kenya. This deterministic model represents a simplified representation of HIV and demographics in Kenya.

2.2 | CVD microsimulation model

The underlying structure of our CVD microsimulation is based on a recently published cost-effectiveness analysis of CVD management in Kenya [11]. To quantify the epidemiological and economic burden of hypertension and diabetes, we focused on the subsequent effect of these conditions on the incidence of major CVD events that could result in death or disability. For this purpose, we used the individual-level data from the 2015 Kenyan STEPwise survey [10] and estimated the 10-year risk of first CVD event for surveyed individuals via the Framingham calculator [12] (Figure 1A). The Framingham calculator was developed in North America and may not fully generalize to Kenya, but no other simple calculators based on African populations exist.

Next, we defined eight risk categories (Table 1) based on binary classifications of Framingham-calculated 10-year CVD risk (greater or less than 10%), hypertension (blood pressure greater or less than 140/90 mmHg) and Type 2 diabetes status (present or absent), and estimated the population proportion falling within each risk-category by strata of sex and five-year age categories (sex/age). We adjusted these estimates to match the reported prevalence of hypertension and diabetes at a national and regional level in 2015. Our underlying goal in defining these risk categories was to develop a composite measure of individual-level risk for future CVD events—as a function of hypertension and diabetes status—which could represent the distribution of risks at a population level. Simulated individuals enter the model with an initial risk category determined according to the population risk profile. As individuals age with time, the model allows for transitions to higher risk categories.

We assumed that individuals falling within each risk category experience certain probabilities of future CVD events related to cardiovascular heart disease (CHD) (cardiac arrest, myocardial infarction [MI] or angina) and stroke. The risk of first CHD and stroke for each age, sex and ten-year risk stratum was derived from corresponding Framingham calculators [13,14]. Effective treatment for hypertension and diabetes are assumed to reduce the risk of both initial and subsequent CHD and stroke events; we thus conservatively ignore the benefits of such treatment on other events such as microvascular complications of diabetes. Table 2 provides a list of modelling parameters (Data S1).

2.3 | Hybrid HIV/CVD model

Figure 1C shows the logical relationship and flow of information within the hybrid HIV/CVD model. The microsimulation is coded in C++, and runs in discrete time steps representing one year. Main outcomes are reported as median values and 95% uncertainty ranges across 2,000 random simulations. Due to limited space, the results are presented in terms of median values throughout the text and 95% uncertainty ranges (when available) are provided in corresponding tables in each section.

The initial population is generated according to outputs from the Spectrum model at the end of year 2018, and is characterized in terms of HIV prevalence and ART coverage by sex and age (reported as five-year age categories). The microsimulation starts in year 2019 and runs to 2033.

Annual CVD dynamics are modelled directly at the individual-level as described above. HIV dynamics are modelled at a population-level via the Spectrum model, and the projected annual number of new HIV infections and HIV-related deaths by sex/age is imported into the hybrid model. Finally, the additional probability of death due to non-HIV/non-CVD causes is estimated by subtracting the simulated number of HIV and CVD deaths from the projected number of all-cause deaths in

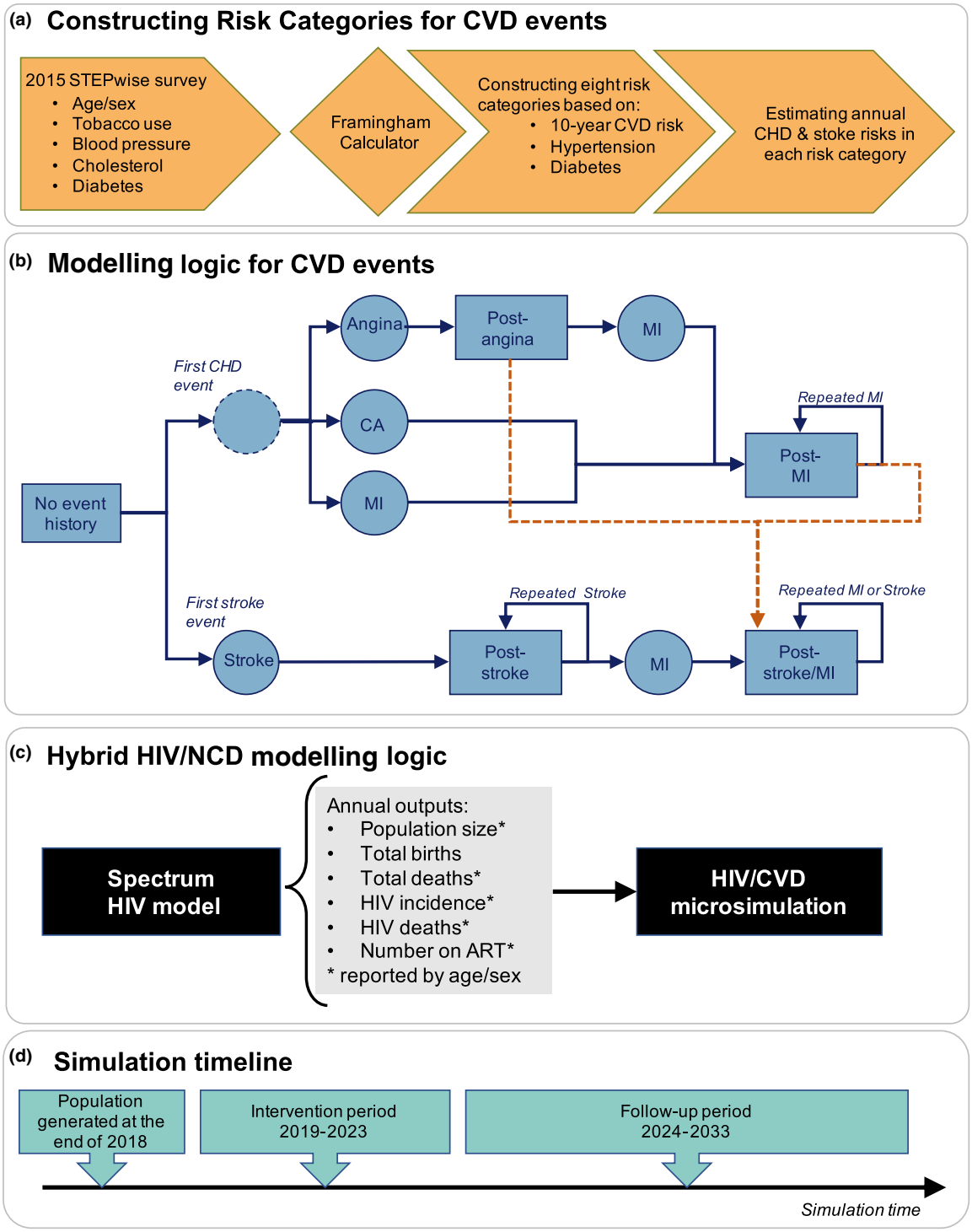

Figure 1. Hybrid HIV/CVD model overview.
Panel A illustrates the method for defining eight cardiovascular disease (CVD) risk categories using data from the 2015 STEPwise survey in Kenya. Panel B shows the schematic model of CVD events, namely cardiac arrest (CA), angina, myocardial infarction (MI) and stroke. Following a CVD event, individuals experience a probability of acute mortality in the first year. If they survive, they subsequently move to a post-event state in which they experience an increased annual risk of mortality, risk of new/repeated CVD events, and disability for future life years lived in the model. Dashed arrows showed in orange mark the risk of stroke among those in post-cardiovascular heart disease (CHD) states. Panel C shows the relationships and flow of information between Spectrum and the HIV/CVD microsimulation. Panel D shows the simulation timeline, starting in year 2019 and ending in 2033. Annual outputs from the Spectrum model are used to inform the demographic processes and HIV dynamics in the HIV/CVD microsimulation. To ensure a precision of results, the baseline and intervention scenarios are modelled across 2000 random simulations. All outcomes are reported as median values across these simulations.

Table 1. CVD risk group stratification based on 10-year CVD risk, hypertension and diabetes status[a]

CVD risk category	Low CVD risk (<10%)[b]	Hypertension[c]	Diabetes[d]
Risk category 1	Yes	No	No
Risk category 2	No	No	No
Risk category 3	Yes	Yes	No
Risk category 4	No	Yes	No
Risk category 5	Yes	No	Yes
Risk category 6	No	No	Yes
Risk category 7	Yes	Yes	Yes
Risk category 8	No	Yes	Yes

[a]Cardiovascular diseases (CVDs).
[b]Ten-year CVD risk as estimated by the Framingham calculator [12].
[c]Individuals with systolic blood pressure ≥ 140 and/or diastolic blood pressure ≥ 90 are assumed to have hypertension.
[d]Individuals with a plasma venous value ≥ 7.0 mmol/L (126 mg/dL) or currently on blood glucose lowering medication are assumed to have diabetes. The Kenya 2015 STEPwise approach to Surveillance (STEPS) survey data is not reported separately for type 1 and type 2 diabetes. Given the low prevalence of type 1 diabetes in Kenya (at ~ 10-15% of total diabetes) and low prevalence of diabetes in the survey (~1.9% among both sexes), we assumed that the reported data represents type 2 diabetes.

Spectrum and dividing by the population size in each sex/age stratum in each year (Data S1).

2.4 | HIV/CVD Regional analysis

We expanded our national model of HIV/CVDs in Kenya to represent three regions including Nairobi, Coast and Central (Data S1). Each regional model was informed using estimates from the corresponding Spectrum model as discussed above. Given the lack of estimates from AIM on the impact of HIV interventions at the regional level, we used the national Spectrum model to estimate intervention's impact. We then applied these estimates to the regional models, weighted by sex/age, to project the future size of the HIV epidemic and the number of HIV-related deaths in each region.

2.5 | Modelled intervention

Following the framework of project SEARCH [15], we modelled a joint community outreach campaign for screening and treatment of HIV, hypertension and diabetes over five consecutive years (2019–2023), and followed the population for a decade after the end of the intervention to year 2033. To reflect ambitious but potentially feasible implementation, we assumed that the intervention targets 20% of the population in geographically distinct communities on an annual basis, and can reach up to 90% of eligible adults (aged 15+) who are assumed to undergo screening for HIV, hypertension and diabetes [16]. The average ART uptake (i.e. accounting for loss to care and re-engagement in care) was estimated at 73% for those HIV-infected individuals with no previous/current ART use [5,17].

To determine the impact of treatment for hypertension and diabetes, we estimated the average decrease in risk of future CVD events provided by long-term treatment. Specifically, we assumed that treatment for hypertension would result in an average 10-mmHg reduction in systolic blood pressure [18], and that treatment for diabetes would consist of metformin, a widely available and inexpensive first-line treatment for diabetes [19] (Table 2). At baseline, we assumed that 50% of all individuals newly diagnosed with hypertension or diabetes would remain consistently in care (i.e. that the intervention would meet 50% of the total time needed to successfully complete NCD treatment); this number was assumed to incorporate both incomplete linkage to care and net losses to follow-up (disengagement minus re-engagement) over time and was varied in sensitivity analysis.

The intervention scenario was compared against a baseline model in which ART coverage in 2018 (final year of data) was maintained at a fixed level from 2019 to 2033, and lifetime medication management for NCDs was kept to minimal levels [20-22] (Data S1).

2.6 | Cost-effectiveness analysis

Cost analyses from the SEARCH study provided estimates of disease screening and ART treatment [7,37]. Costs of standard care for CVD-related events were based on those estimated from public/semi-public healthcare facilities in Kenya [11]. All healthcare costs were reported in the year in which they occurred. For each scenario, disability-adjusted life years (DALYs) were estimated as years lost to HIV- or CVD-related disability and years of life lost to premature mortality. The cost-effectiveness ratio was reported at the end of simulation period (year 2033) and was assessed against a threshold of $2,010 corresponding to Kenya's 2019 per-capita gross domestic product (GDP) [38]. In addition, we considered alternative cost thresholds (at increments of $500 per DALY) that reflect more stringent willingness-to-pay thresholds for health interventions (Data S1).

2.7 | Sensitivity analysis

One-way sensitivity analysis was performed by varying the value of selected parameters to +/-15% of the original values (Table 2). For each analysis, we evaluated the changes in main outcomes in the national model, comparing integrated HIV/NCD scenario to the baseline (status-quo) scenario.

3 | RESULTS

3.1 | Population summary

The simulated populations were generated based on projections from Spectrum at a national- and regional level in 2018 (Table 3). The national Spectrum model estimated a population size of 50.9 million, an HIV prevalence of 3.3% (2.4% among men and 4.3% among women) and ART coverage of 68% among those in need of ART. This translated to an HIV incidence of 0.97 per 1000 person-years, corresponding to 16,419 and 30,020 new infections among men and women in 2018. The regional models reflected known heterogeneities in the burden of HIV and NCDs at local level, with the highest

Table 2. CVD microsimulation model parameters[a]

Parameter	Value	Reference
CVD natural history[b]		
Probability of first CHD event type		
Cardiac arrest	10%	
MI	32% (males)/ 20% (females)	[23]
Angina	1 - probability of other events	[24]
Acute (one-year) mortality following a CVD event		
Cardiac arrest	0.95	[25]
MI	0.05	[26]
Angina	0.045	[27]
Stroke	0.38	[28]
Annual mortality (post-event)		
MI	0.04	[29]
Angina	0.03	[29]
Stroke	0.05	[29]
Annual risk of new event in post-event states		
Repeated MI post-MI	0.064	[30]
MI post-angina	0.035	[31]
Repeated stroke post-stroke	0.04	[32]
Intervention characteristics[c]		
Annual screening coverage	20% of population	Assumption
Screening success	90%	[16]
NCD treatment uptake & long-term medication management	50%	Assumption
NCD treatment effectiveness[c,d]		
% reduction in CHD events with hypertension treatment among people		[18]
- With diabetes	88%	
- Without diabetes	77%	
% reduction in stroke events with hypertension treatment among people		[18]
- With diabetes	74%	
- Without diabetes	74%	
% reduction in CHD and stroke events with diabetes treatment	79%	[19]
Costs (2018 USD)[c]		
Acute care for cardiac arrest	1,049.14	[33]
Acute care for MI	2,041.02	[33]
Acute care for angina	1,264.90	[33]
Acute care for stroke	1,916.26	[33]
Non-acute care post-CHD	331.15 per year	[34]
Non-acute care post-stroke	993.44 per year	[34]
Screening for HIV	21.50	[7]
Screening for hypertension and diabetes	1.22	[7]
HIV treatment (ART)	297.51 per year	[35]
Hypertension treatment	77.65 per year	[33]
Diabetes treatment	186.73 per year	[33]
Disability weights[c]		
Angina	0.08	[36]
Cardiac arrest	0.08	
MI	0.08 (first year)	
	0.072 (subsequent years)	
Stroke	0.152	
HIV	0.078 (on ART)	
	0.274 (off ART)	

[a]Non-communicable diseases (NCD); Cardiovascular diseases (CVDs); Cardiovascular heart disease (CHD); Myocardial infarction (MI).
[b]The underlying structure of CVD natural history model and selected parameter values are based on Subramanian et al. (2019) [11].
[c]Parameters are varied within +/- 15% of their original values in sensitivity analysis.
[d]NCD treatment effectiveness is estimated separately for hypertension and diabetes treatment, and the impact of combined treatments is modelled as independent and multiplicative (Data S1).

HIV incidence (1.09 per 1000 person-years) in Nairobi region and the highest hypertension prevalence (37.5%) in the Central region.

3.2 | HIV-related outcomes

In the status-quo scenario (maintaining ART coverage to reported levels at the end of year 2018), the HIV incidence in Kenya was projected to fall by 26% (ranging from 22% in Coast to 26% in Nairobi region) from 2019 to 2033 (Table 4). Increasing ART coverage to 88% of all people diagnosed with HIV by 2033 resulted in HIV incidence to fall by 64% within the same period. Compared to baseline, this corresponded to averting 347,000 HIV infections and 289,000 HIV deaths in Kenya by 2033. At a regional level, the absolute impact of expanded HIV services was highest in Nairobi, averting 42,000 HIV infections and 37,000 HIV deaths compared to baseline. However, the efficiency of expanded ART was highest in Coast region, with 0.06 HIV infections averted per additional person-year on ART. Despite the large reductions in HIV incidence and mortality under expanded ART, HIV prevalence remained relatively stable, reflecting better survival among individuals consistently on ART.

3.3 | NCD-related outcomes

At a national level and in the absence of expanded treatment for HIV, Diabetes and Hypertension, the model projected the prevalence of untreated hypertension and diabetes at 32.43% and 4.27% respectively by 2033 (Table 5). The HIV/NCD integrated screening covered estimated 5.5 million individuals annually from 2019 to 2023, diagnosing over 8.5m individuals with hypertension and 0.83 m with diabetes (Figure 2A). Assuming that these diagnoses result in treatment for 50% of subsequent eligible treatment time, the intervention was

Table 3. Baseline simulated population

Simulated population in 2018	National	Nairobi region	Central region	Coast region
Population size[a]	51.0 million	4.9 million	4.3 million	5.1 million
HIV prevalence[a]	3.35%	4.23%	3.19%	2.65%
ART coverage[a]	68.26%	67.88%	63.71%	68.71%
HIV incidence (per 1000/year)[a]	0.97	1.09	1.06	0.66
Hypertension prevalence[b]	24.1%	14.1%	37.5%	19.8%
Diabetes prevalence[b]	2.13%	3.84%	2.71%	2.01%

[a]Population size and HIV outcomes were projected by the national and regional Spectrum AIDS Impact Models (AIM), calibrated to the 2019 official HIV estimates from national AIDS control council. Given the deterministic nature of the model, no information is available on uncertainty ranges.
[b]The baseline prevalence of hypertension and diabetes in each model were calibrated to estimated values from the Kenya 2015 STEPwise approach to Surveillance (STEPS) survey respectively. The prevalence is shown for individuals between the ages of 15 to 70 years, similar to the STEP survey. Values represent the median values across 2,000 simulations (uncertainty ranges were too small to show).

projected to reduce the prevalence of untreated hypertension to 27.51% and of untreated diabetes to 3.42% by 2033. This resulted in averting 116,600 CVD events and 43,600 CVD deaths by 2033. At a regional level, the intervention impact was highest in the Central region, averting 22,200 CVD events and 8300 CVD deaths over the next 15 years.

3.4 | Cost-effectiveness analysis

At a national level, the incremental costs of HIV/NCD integrated programme was estimated at $6.68b over 15 years (Table 6). This reflected additional costs needed for: 5 years of screening for HIV ($0.6b) and hypertension and diabetes ($0.03b); increased treatment costs for HIV ($1.18b), diabetes ($1.28b) and hypertension ($3.95b); as well as costs saved for CVD care ($-0.35b) (Table 6; Figure 3). The intervention was estimated to avert 7.76m DALYs, for an incremental cost-effectiveness ratio of $860 per DALY averted at the national-level. At a regional level, the intervention resulted in highest incremental costs in the Central region ($945m) and saved the most DALYs in Nairobi (840,000). The cost per DALY averted was $754 in Nairobi, $818 in the Coastal region, and $1500 in the Central region, all below the per capita GDP of $2010 in Kenya.

Using the threshold of $2010 per DALY averted, the probability that the intervention would be cost-effective was 91.8% at a national level, ranging from 71.28% in Central to 91.35% in Nairobi. As policy makers may prefer different willingness-to-pay thresholds, [39] we explored other thresholds through sensitivity analyses (Figure 3). Lowering the willingness-to-pay threshold to $1,000 reduced the probability of cost-effectiveness to 59% at a national level, while increasing the heterogeneity at a regional level (with probabilities ranging from 70% in Nairobi to 55% in Coast and only 5% in the Central region). The intervention did not remain cost-effective under a threshold $500.

3.5 | Sensitivity analysis

All outcomes were sensitive to variation in value of parameters related to NCD screening/treatment coverage (e.g. annual screening coverage, screening success rate and NCD treatment uptake) (Figure 4). The epidemiological impact of intervention (measured by the number of CVD events and deaths averted) was also sensitive to variation in NCD treatment effectiveness (modelled as reduction in risk of CHD and stroke). The incremental costs were also sensitive to variation in cost of hypertension and diabetes treatment, comprising the biggest portion of intervention costs. With < 4% variations, DALYs were robust to variation in value of selected parameters, suggesting that the majority of DALYs in this population was due to HIV infection.

4 | DISCUSSION

Integrated, population-based screening and treatment for HIV and NCDs in Kenya could have substantial impact over 15 years, averting 64% of new HIV infections, 284,000 HIV-related deaths, 43,600 CVD-related deaths, and 7.8 million HIV- and CVD-related DALYs. At a commonly used threshold for cost-effectiveness (less than per capita GDP per DALY averted), this intervention was more than 90% likely to be cost-effective. However, the cost required to fully scale up this intervention was substantial, with a 15-year incremental cost of $6.7 billion dollars, equivalent to an increase of 12% in Kenya's total health budget [40]. These results illustrate that integrated HIV/NCD diagnosis and management has the potential to be highly impactful and moderately cost-effective in a country like Kenya, but achieving these gains will only be possible with sustained financial and political commitment.

Our regional models reveal important geographic variation. Compared to the national estimate, the cost per DALY averted (for HIV and NCDs) was 74% higher in the Central region, where the prevalence was higher for hypertension but lower for HIV. These results are in line with previous reports of health disparities across counties in Kenya [41]. In scaling up integrated HIV/NCD care, therefore, the most efficient use of resources may be to first focus integration efforts on those regions with higher HIV prevalence, while maintaining separate HIV and NCD systems (i.e. focusing NCD management on older and other high-risk populations [42]) in settings where NCD prevalence is high but HIV prevalence is low.

Both overall costs and cost-effectiveness were highly sensitive to the cost of hypertension management, owing to the high prevalence of hypertension in this population (ranging from 2.3 times the prevalence of HIV in Nairobi region to 7.6 times HIV prevalence in Central region). We assumed that management of hypertension would cost $78 per person-year, similar to other public-sector studies in sub-Saharan Africa [33,42] but lower than at least one estimate from Oyando et al. ($304 per person-year)[43]. In a study of five rural counties in Western Kenya, Osetinsky et al. [44] find the cost of chronic disease medicine programmes to be lowest compared to other public NCD care programmes. However, the estimated per patient annual cost of NCD care in these programmes ($27.50 to

Table 4. Summary of HIV-related outcomes in Kenya[a]

	National		Nairobi region		Central region		Coast region	
	Baseline	**Intervention**	**Baseline**	**Intervention**	**Baseline**	**Intervention**	**Baseline**	**Intervention**
ART coverage								
Proportion of people living with HIV on ART in 2033	68.26%	88.21%	67.88%	87.39%	68.71%	87.50%	63.71%	85.75%
Total number on ART from 2019 to 2033 (million)	37.46 [32.20 to 53.10]	45.86 [38.3 to 62.70]	4.87 [4.20 to 6.90]	5.94 [5.00 to 8.10]	2.78 [2.40 to 3.90]	3.36 [2.80 to 4.60]	2.98 [2.60 to 4.20]	3.56 [3.00 to 4.90]
Additional person year on ART (million)		8.40 [6.20 to 10.10]		1.07 [0.80 to 1.30]		0.58 [0.40 to 0.70]		0.58 [0.40 to 0.70]
HIV incidence (per 1000/year)								
2018	0.97 [0.59 to 1.68]		1.09 [0.67 to 1.89]		0.66 [0.40 to 1.14]		1.06 [0.65 to 1.84]	
2033	0.72 [0.52 to 1.37]	0.35 [0.28 to 0.59]	0.81 [0.59 to 1.54]	0.39 [0.31 to 0.65]	0.51 [0.37 to 0.97]	0.25 [0.20 to 0.42]	0.83 [0.60 to 1.58]	0.39 [0.31 to 0.65]
% Reduction	25.77% [7.10% to 45.48%]	63.92% [48.29% to 66.06%]	25.69% [7.07% to 45.33%]	64.22% [48.52% to 66.37%]	22.73% [6.26% to 40.11%]	62.12% [46.93% to 64.20%]	21.7% [5.98% to 38.29%]	63.21% [47.76% to 65.32%]
HIV prevalence								
2018	3.35% [2.87% to 4.26%]		4.23% [3.62% to 5.37%]		2.65% [2.27% to 3.37%]		3.19% [2.73% to 4.05%]	
2033	2.43% [1.80% to 3.78%]	2.33% [1.73% to 3.62%]	2.99% [2.22% to 4.65%]	2.88% [2.14% to 4.48%]	2.03% [1.51% to 3.16%]	1.96% [1.45% to 3.05%]	2.37% [1.76% to 3.69%]	2.15% [1.60% to 3.34%]
% Reduction	27.55% [20.50% to 30.62%]	30.39% [26.58% to 32.33%]	29.35% [21.84% to 32.62%]	31.89% [27.89% to 33.93%]	23.41% [17.42% to 26.01%]	25.99% [22.73% to 27.65%]	25.54% [19.00% to 28.28%]	32.53% [28.45% to 34.61%]
New HIV infections								
Total from 2019 to 2033 (thousands)	734.27 [521.75 to 1,261.79]	387.55 [317.42 to 637.93]	87.01 [61.82 to 149.52]	44.87 [36.75 to 73.85]	49.45 [35.13 to84.97]	25.7 [21.05 to 42.30]	71.28 [50.64 to 122.49]	36.56 [29.94 to 60.18]
Infections averted (thousands)		346.73 [196.79 to 629.64]		42.15 [23.92 to 76.54]		23.76 [13.48 to 43.15]		34.72 [19.70 to 63.05]
Infections averted per additional ART person/ year		0.041		0.039		0.041		0.06
HIV deaths								
Total from 2019 to 2033 (thousands)	544.61 [449.49 to 619.60]	255.86 [217.87 to 295.29]	69.54 [57.39 to 79.11]	32.82 [27.94 to 37.88]	41.76 [34.46 to 48.51]	21.77 [18.53 to 25.12]	45.13 [37.24 to 51.34]	23.91 [20.36 to 27.59]
Deaths averted (thousands)		288.76 [231.79 to 342.25]		36.72 [29.47 to 43.52]		19.99 [16.04 to 23.69]		21.22 [17.03 to 25.15]

Table 4. (*Continued*)

	National		Nairobi region		Central region		Coast region	
	Baseline	**Intervention**	**Baseline**	**Intervention**	**Baseline**	**Intervention**	**Baseline**	**Intervention**
Deaths averted per additional ART person/year		0.034		0.034		0.034		0.036

[a]HIV-related outcomes are projected by the Spectrum model for the baseline and intervention at a national and regional level. Models are initialized with a similar population in 2018 and are followed to year 2033. The baseline scenario assumes a fixed ART coverage at 2018 levels over time. The intervention scenario models a gradual increase in coverage of ART from 2019 to 2023 [assuming a fixed coverage afterwards, from year 2024 to 2033). Values represents the median value [95% uncertainty ranges]. Uncertainty ranges are estimated across 1000 random simulations (generated by permuting epidemiological and behaviour parameters), weighted and resampled based on goodness of fit to the historical prevalence data (see Section 1.4 in Data S1).

Table 5. Summary of NCD-related outcomes in Kenya[a,b]

	National	Nairobi region	Central region	Coast region
NCDs prevalence in 2033[c]				
Baseline:				
Untreated hypertension	32.43% [32.40% to 32.45%]	25.94% [25.91% to 25.97%]	47.89% [47.86% to 47.91%]	26.41% [26.39% to 26.44%]
Untreated diabetes	4.27% [4.25% to 4.28%]	9.75% [9.73% to 9.77%]	6.05% [6.04% to 6.07%]	3.4% [3.39% to 3.42%]
Intervention:				
Untreated hypertension	27.51% [27.48% to 27.53%]	22.61% [22.58% to 22.63%]	38.73% [38.7% to 38.76%]	22.58% [22.55% to 22.61%]
Untreated diabetes	3.42% [3.41% to 3.44%]	8.43% [8.41% to 8.45%]	4.43% [4.42% to 4.45%]	2.79% [2.78% to 2.8%]
CVD events averted (2019 – 2033)				
MI	24,900 [17,900 to 31,300]	1600 [1000 to 2300]	4900 [4,100 to 5,700]	2000 [1,400 to 2,600]
Angina	12,500 [7,800 to 17,000]	1200 [700 to 1600]	3000 [2400 to 3500]	1100 [700 to 1500]
Cardiac Arrest	3200 [1200 to 5100]	200 [0 to 400]	500 [300 to 800]	200 [0 to 400]
Stroke	76,000 [66,400 to 86,100]	6200 [5300 to 7200]	13,800 [12,500 to 14,900]	5300 [4300 to 6200]
Total	116,600 [104,300 to 128,300]	9200 [8100 to 10,300]	22,200 [20,600 to 23,700]	8600 [7500 to 9800]
CVD deaths averted (2019 to 2033)				
MI	4800 [2200 to 7500]	300 [0 to 600]	1000 [700 to 1300]	1000 [700 to 1300]
Angina	1,500 [−700 to 3700]	100 [−100 to 400]	400 [200 to 700]	400 [200 to 700]
Cardiac Arrest	3000 [1000 to 4800]	200 [0 to 400]	500 [300 to 700]	500 [300 to 700]
Stroke	34,200 [27,700 to 41,000]	2800 [2100 to 3400]	6400 [5600 to 7200]	6400 [5600 to 7200]
Total	43,600 [3,6400 to 50,400]	3400 [2700 to 4100]	8300 [7500 to 9100]	8300 [7500 to 9100]

[a]Non-communicable diseases (NCD); Cardiovascular disease (CVD); Myocardial infarction (MI).
[b]NCD-related outcomes are projected by the HIV/NCD microsimulation for the baseline and intervention at a national and regional level. Models are initialized with a similar population in 2018 and are followed to year 2033. The baseline scenario assumes minimal NCD treatment. The intervention scenario models an annual campaign for screening and treatment on NCDs running from 2019-2023. Values represents the median [95% uncertainty ranges] across 2000 random simulations.
[c]See Data S1 for the uncertainty around the number people with untreated diabetes and hypertension in the initial and final cohort.

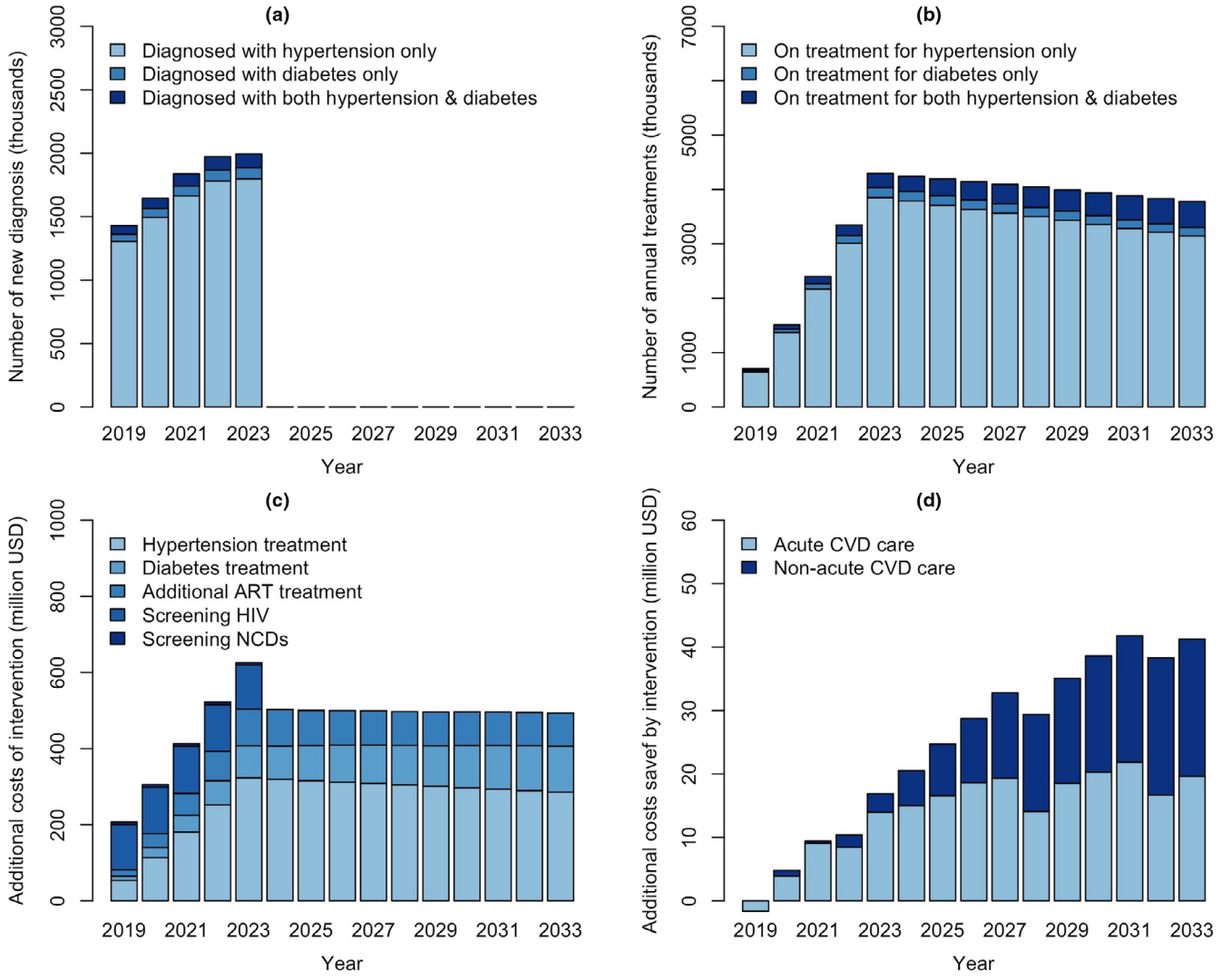

Figure 2. Projected outcomes from combined HIV/NCD diagnosis and management in Kenya.
The intervention runs from 2019-2023, screening 20% of the population on an annual basis for HIV, hypertension and diabetes. Panel A shows the annual number of people diagnosed with hypertension and/or diabetes. The intervention further provides treatment to a proportion of those diagnosed with HIV, hypertension and/or diabetes. Panel B shows the number of individuals receiving treatment for hypertension and/or diabetes over time. Costs are divided into two groups, including additional costs required for disease screening and treatment (Panel C) and costs saved by averting future CVD events (Panel D). ART, antiretroviral therapy; NCD, non-communicable diseases; CVD, cardiovascular disease.

$154.06) was still higher than the per capita healthcare budget contributions ($17.50 to $20.00) in these counties, suggesting a large gap in budget for expanding and sustaining NCD care even via most efficient care delivery models. In our study, the costs of hypertension management accounted for over 60% of total costs, but CVD deaths accounted for only 15% of all deaths averted; thus, at this cost, HIV care appears much more cost-effective than NCD management. Mounting a national effort to manage hypertension and diabetes may hinge on cost minimization, which may include strategies from the HIV response where the cost of first-line HIV medications decreased by 99% from $10,000 per person in 2000 to $116 per person in 2010 [45,46].

As with any modelling study, this analysis has important limitations. First, both Spectrum and our NCD model employ a number of simplifying assumptions (e.g. heterogeneous mixing within risk groups, estimating region-level impact of HIV interventions as reflective of national-level estimates, CVD risk within fixed categories) that do not fully capture the complex interplay between HIV and NCDs in Kenya. Second, we estimated CVD risk using the Framingham calculator, which allows for simple estimation of risk with a small number of input parameters and was calibrated to a largely white male population and may not accurately estimate CVD risk in African populations [47]. As genetics also play a role in NCD risks and Africa has genetically and ethnically diverse populations [48,49], further studies (e.g. using potential electronic health records) determine better prediction models for NCD-risk-profiles in African populations. Third, by focusing only on stroke and major CHD events, our model ignores other positive benefits of treating hypertension and diabetes (for example,

Table 6. Costs and DALYs required/saved by the integrated HIV and NCD care in Kenya[a,b]

	National	Nairobi region	Central region	Coast region
Saved costs (2018 US dollars)				
Acute CVD care	0.22 [0.19 to 0.24] billion	16.94 [14.77 to 19.01] million	40.70 [37.72 to 43.45] million	15.85 [13.64 to 18.02] million
Non-acute CVD care	0.15 [0.11 to 0.20] billion	14.33 [10.43 to 18.56] million	32.18 [26.82 to 37.56] million	11.08 [7.02 to 18.02] million
Additional costs (2018 US dollars)				
ART	1.18 [1.17 to 1.20] billion	133.71 [132.20 to 135.16] million	83.81 [82.45 to 85.13] million	91.16 [89.83 to 92.51] million
Diabetes treatment	1.28 [1.27 to 1.29] billion	211.9 [210.67 to 213.23] million	207.46 [206.27 to 208.58] million	84.18 [83.36 to 84.98] million
Hypertension treatment				
Screening for HIV	603.34 [603.12 to 603.58] million	62.03 [62.00 to 62.05] million	67.63 [67.61 to 67.65] million	50.56 [50.54 to 50.59] million
Screening for diabetes and hypertension	34.24 [34.22 to 34.25] million	3,519.73 [3,521.09 to 3,518.35] thousand	3,837.83 [3,839.01 to 3,836.62] thousand	2,869.06 [2,870.42 to 2,867.70] thousand
Total Costs (2018 US dollars)				
Incremental costs	6.68 [6.61 to 6.74] billion	632.95 [626.79 to 638.75] million	945.29 [937.44 to 93.05] million	471.59 [466.08 to 476.99] million
Total DALYs				
Incremental DALYs averted	7.76 [8.01 to 7.51] million	839.13 [811.93 to 865.24]	632.88 [608.74 to 657.06]	576.82 [547.86 to 604.93]
Incremental costs per DALY (2018 USD)				
	860.36 [830.59 to 890.66]	754.04 [729.63 to 780.26]	1,493.07 [1,435.63 to 1,555.65]	818.01 [864.38 to 776.50]

[a]Non-communicable diseases (NCD); Disability-adjusted life year (DALY); Cardiovascular disease (CVD).
[b]Values represent the differences in simulated costs and DALYs between the baseline and intervention at a national and regional level. Future costs are discounted at 3%. Values represents the median [95% uncertainty ranges] across 2,000 random simulations.

reductions in microvascular complications of diabetes). Thus, our estimates of DALYs averted may be conservative. Fourth, in the absence of accepted cost-effectiveness thresholds, we benchmarked cost-effectiveness primarily against Kenya's per-capita GDP. Recent arguments [50] suggest that per-capita GDP thresholds may result in labelling a number of unaffordable interventions as "cost-effective"; to the extent that Kenya's true willingness or ability to pay for health interventions is lower, our model may be overly optimistic in its estimates of cost-effectiveness. Fifth, we did not account for dynamic changes in CVD risk (within sex/age stratum) over time. As trends in smoking and dietary intake change in Kenya [51-54], our estimates of future CVD risk may be underestimated or overestimated. Finally, some of our estimates (e.g. estimated population in specific low-probability CVD risk categories, particularly at the regional-level) are based on small sample sizes and thus subject to substantial uncertainty.

5 | CONCLUSIONS

We have constructed a model to evaluate the likely population-level impact and cost-effectiveness of a potential integrated HIV/NCD diagnosis and management programme based on that of Project SEARCH in Kenya. We find that such an integrated programme could save more than 300,000 lives over a 15-year period, with substantial improvements in the dual epidemics of HIV and NCDs in this setting. Such a programme could be moderately cost-effective; cost-effectiveness could be substantially improved by lowering the cost of hypertension management. Important variations also existed at the subnational-level, arguing for a targeted approach to HIV/NCD integration that first focuses on regions with higher HIV prevalence. These findings are likely to generalize to other East African countries with similar epidemiology and economic conditions and may inform intervention design in sub-Saharan Africa more broadly, though studies of specific interventions in specific contexts are needed. Achieving these gains will only be possible with sufficient political will and ensuring increased financial commitment to support scale-up at the regional and national-levels.

Two decades ago, researchers had shown the epidemiological basis for CVDs control policies in sub-Saharan Africa [55]. Given Kenya's 2030 Health Policy framework and Big 4 Agenda for expanding universal health coverage [56,57], studies showing health insurance to have a positive effect on stemming HIV [58], and increasing affordability for NCDs

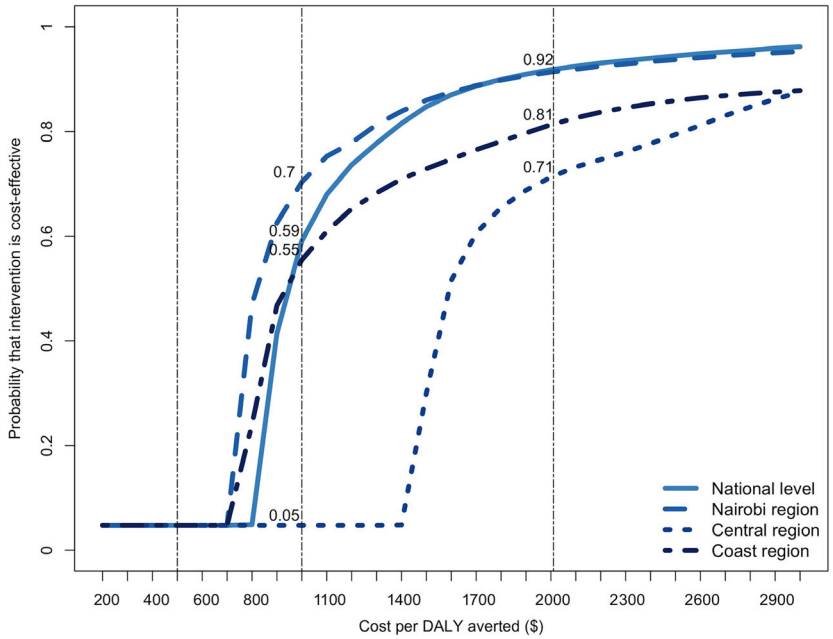

Figure 3. Cost-effectiveness acceptability curves for integrated HIV and NCD diagnosis and management in Kenya.
The x-axis shows the cost per disability-adjusted life year (DALY) averted by the intervention, and the y-axis shows the proportion of stochastic simulations falling below the corresponding cost-effectiveness threshold. Vertical lines represent alternative thresholds for evaluating cost-effectiveness at $500, $1000 and $2010 (Kenya's 2019 per-capita gross domestic product). NCD, non-communicable diseases.

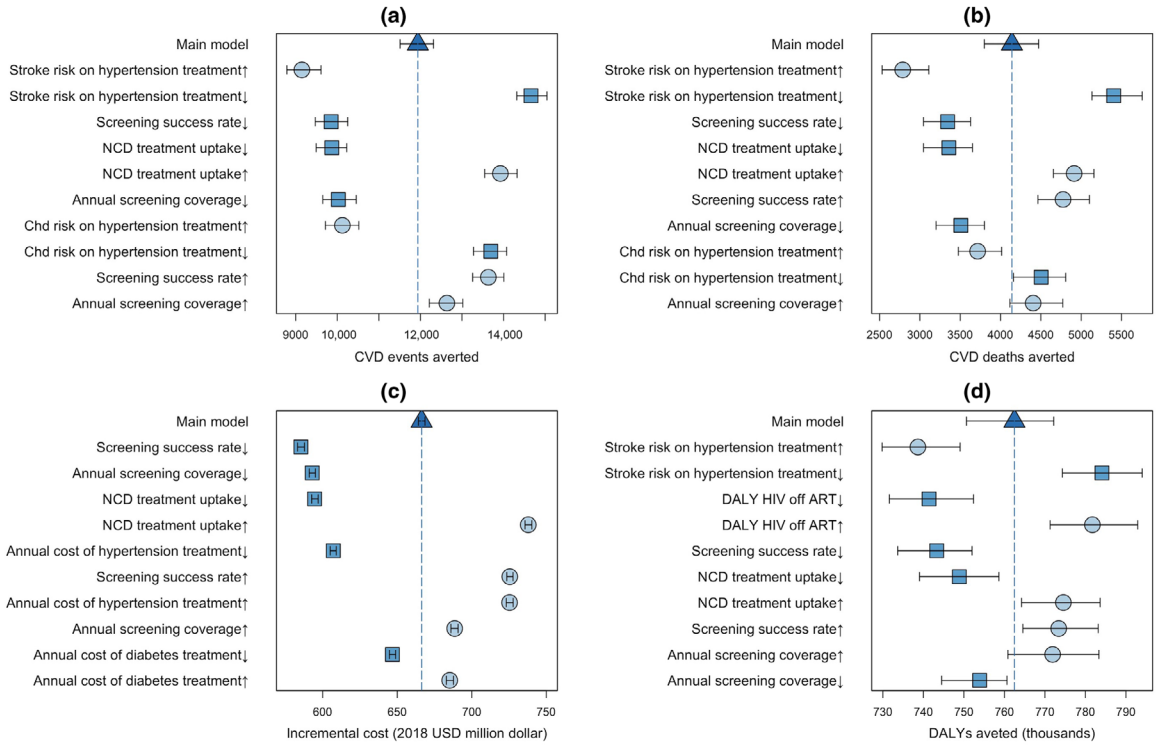

Figure 4. One-way sensitivity analysis to value of selected model parameters.
Panels show the sensitivity of epidemiological outputs, including the number of CVD events (panel A) and deaths (panel B) averted, and costing outcomes, including the incremental cost of intervention (panel C) and DALYs averted (panel D), under one-way variation in the value of selected model parameters. Each parameter value is followed by an up/down arrow, denoting a 15% increase (circle marks) or decrease (square marks) in the input parameter value as listed in Table 3. Each scenario is simulated starting in year 2019 and is followed to year 2033. The bars and arrows represent the median and interquartile ranges across 500 simulations. The triangle mark and dashed line represent the main model with no parameter variation. The results are summarized by showing the ten parameters for which variation resulted in the largest variations from the main model (decreasing impact from top to bottom. CVD, cardiovascular disease; NCD, non-communicable diseases; DALY, disability-adjusted life year; ART, antiretroviral therapy.

treatments [33], studies like ours are useful in advancing such national polices. Results from our modelling study in Kenya emphasize the critical need for an integrated approach to tackle the growing burden of HIV and NCDs over the next decade.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

PK, BW, DD and CB contributed to conception and design. PK, MS, CD, JP and YT contributed to model development. PK, MS, CD and YT contributed to analysis. PK, BW, RW, KM, DD and CB contributed to interpretation and important intellectual input. PK, MS and DD contributed to first draft of manuscript. PK, BW, MS, CD, JP, YT, RW, KM, DD and CB contributed to manuscript review and revision. All authors have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:
Data S1: Supporting information and additional results

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RESEARCH ARTICLE

Cost-effectiveness analysis of integrating screening and treatment of selected non-communicable diseases into HIV/AIDS treatment in Uganda

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Abstract

Introduction: Despite growing enthusiasm for integrating treatment of non-communicable diseases (NCDs) into human immunodeficiency virus (HIV) care and treatment services in sub-Saharan Africa, there is little evidence on the potential health and financial consequences of such integration. We aim to study the cost-effectiveness of basic NCD-HIV integration in a Ugandan setting.

Methods: We developed an epidemiologic-cost model to analyze, from the provider perspective, the cost-effectiveness of integrating hypertension, diabetes mellitus (DM) and high cholesterol screening and treatment for people living with HIV (PLWH) receiving antiretroviral therapy (ART) in Uganda. We utilized cardiovascular disease (CVD) risk estimations drawing from the previously established Globorisk model and systematic reviews; HIV and NCD risk factor prevalence from the World Health Organization's STEPwise approach to Surveillance survey and global databases; and cost data from national drug price lists, expert consultation and the literature. Averted CVD cases and corresponding disability-adjusted life years were estimated over 10 subsequent years along with incremental cost-effectiveness of the integration.

Results: Integrating services for hypertension, DM, and high cholesterol among ART patients in Uganda was associated with a mean decrease of the 10-year risk of a CVD event: from 8.2 to 6.6% in older PLWH women (absolute risk reduction of 1.6%), and from 10.7 to 9.5% in older PLWH men (absolute risk reduction of 1.2%), respectively. Integration would yield estimated net costs between $1,400 and $3,250 per disability-adjusted life year averted among older ART patients.

Conclusions: Providing services for hypertension, DM and high cholesterol for Ugandan ART patients would reduce the overall CVD risk among these patients; it would amount to about 2.4% of national HIV/AIDS expenditure, and would present a cost-effectiveness comparable to other standalone interventions to address NCDs in low- and middle-income country settings.

Keywords: HIV; antiretroviral therapy; non-communicable diseases; hypertension; hypercholesterolaemia; diabetes; cardiovascular diseases; integration; sub-Saharan Africa; Uganda

Additional information may be found under the Supporting Information tab for this article.

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1 | INTRODUCTION

Non-communicable diseases (NCDs) have become a major cause of disability and mortality among people living with HIV (PLWH) in sub-Saharan Africa (SSA) [1]. This is largely due to rapidly increasing rates of risk factors, like hypertension, in PLWH [2,3]. Previous cohort studies in SSA have shown that about 21% of PLWH were hypertensive, 22% had hypercholesterolaemia and 3% were diabetic [4,5]. These high levels of risk factors increase the likelihood of cardiovascular diseases (CVD) such as stroke and ischaemic heart disease (IHD), jointly, and together with the likely direct effect of HIV infection on CVD outcomes [5-8]. Concomitantly, improved viral suppression and life expectancy among PLWH stemming from expanded access to antiretroviral therapy (ART), now offer a greater time window for NCDs to develop to full manifestation as PLWH are ageing [9].

In recent years, there has been a dramatic rise in the incidence of CVD in the HIV-infected population. For example previous studies have estimated a two-fold increase in the 10-year CVD risk among PLWH compared to HIV-negative individuals [10-13]. This can be attributed to

Table 1. Description of the interventions considered for the integration modality selected for screening and treatment of hypertension, hypercholesterolaemia, and diabetes mellitus (DM) within HIV treatment services in Uganda.

Non-communicable disease risk factor	Status quo	Integration modality: screen and treat PLWH receiving ART at the HIV clinic
Hypertension	Few patients are screened for high BP	Full coverage of screening for BP
	Referral of individuals with high BP to hypertension clinic	Full coverage of treatment for individuals with high BP
DM	No patient is managed for DM	Screen and test patients for DM
	Refer patients with symptoms suggestive of DM to specialized clinic	Manage patients diagnosed with DM at the ART clinic
Hypercholesterolaemia	No screening for high total cholesterol	Full coverage of screening for high total cholesterol
	No treatment for patients with high total cholesterol	Full coverage of treatment for patients with high total cholesterol
Screening and treatment coverage	Hypertension (7%), DM (1%), hypercholesterolaemia (10%)	100% of PLWH receiving ART (64% of all PLWH in Uganda)

PLWH: people living with HIV. BP: blood pressure. Hypertension: systolic blood pressure >=140 mmHg and/or diastolic blood pressure >= 90 mmHg. Diabetes mellitus: blood glucose levels >=7.0 mm/L or >= 126 mg/dL. Hypercholesterolaemia: blood total cholesterol >= 5.0 mmol/L or >=190 mg/dL.

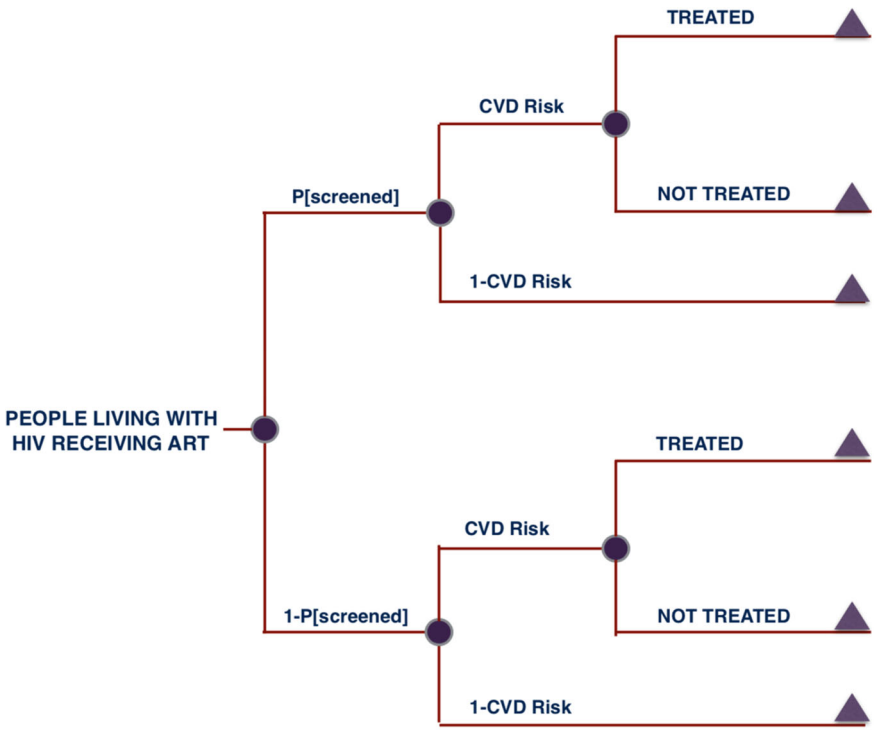

Figure 1. Simple decision tree describing the integration of cardiovascular disease (CVD) risk factor screening and treatment within HIV services in Uganda. The figure illustrates the differential cascade of care between patients (i.e. people living with HIV on ART) screened and those patients not screened for risk factors. CVD Risk: prevalence of CVD risk factors among people living with HIV receiving antiretroviral therapy (ART). P[screened]: percentage of people living with HIV receiving ART who are screened for hypertension, hypercholesterolaemia and diabetes mellitus. In the integration intervention scenario, P[screened] = 100% is assumed. Both branches of the decision-tree model (screened vs. non-screened patients) assume a constant state of non-communicable diseases over the modelled time horizon (i.e. 10 years from integration start).

the complex interplay of the inflammatory effect of HIV infection on the vascular walls, the increased prevalence of traditional risk factors such as hypertension, diabetes mellitus (DM), and hypercholesterolaemia, the adverse effects of some of highly active ART drug regimens, and the large disparities in access to timely screening and treatment of risk factors [6,12,14-19]. In Uganda, where about 6% of the adult population lives with HIV [20], less than 7% of PLWH

with hypertension have access to appropriate treatment [21]. Therefore, integration of routine screening and management of NCDs in HIV care and treatment settings offers an opportunity to curb the emerging NCD crisis that could otherwise jeopardize the health and economic benefits reaped through ART scale-up. Indeed, integrating selected NCD services into ART delivery could leverage the past investments made towards HIV services to, additionally and effectively, deliver NCD treatment services and further reduce preventable deaths among PLWH by achieving economies of scope [22,23].

In integrating screening and treatment of basic NCDs into ART delivery in SSA, the little evidence available so far supports the selection of appropriate NCD interventions to be added to current ART delivery practices. A few studies have examined the clinical benefits and cost implications of fully integrating screening, treatment and long-term monitoring of risk factors like hypertension and hypercholesterolaemia among HIV-infected patients [22-24]. A number of economic evaluations have also studied integrating NCD and HIV services; yet, they are often limited to screening and identifying basic risk factors, like hypertension, without covering the full cascade of NCD treatment (e.g. prevention of CVD) [25].

In this paper, we develop a cost-epidemiologic model to study the health impact, costs and cost-effectiveness of integrating basic screening and treatment services for hypertension, DM and hypercholesterolaemia in HIV treatment services in Uganda.

2 | METHODS

We examined the potential costs and health benefits associated with the integration of screening and treatment for hypertension, DM and hypercholesterolaemia, into HIV treatment services among PLWH receiving ART, compared to the current status quo (low coverage of NCD screening and treatment, see Table 1) in Uganda. We hypothetically evaluate outcomes (costs and health benefits) 10 years into the future (e.g. over 2017 to 2026) after NCD-HIV integration start.

2.1 | Intervention description

Compared with the status quo, integration would introduce treatment of PLWH receiving ART in public HIV clinics who were screened positive for NCDs. Public HIV clinics (within health facilities) are the designated point of care that offers HIV-related services in Uganda. Such clinics provide non-HIV services depending on the health facility level (e.g. in higher level facilities, another point of service for NCD care would exist). Most public clinics schedule services for specific conditions on particular days. For example a diabetic PLWH might not access services for diabetes during an ART pick up visit. She or he would instead have to return on a specific day of the week when the clinic offers diabetes services. The intervention – routine screening and treatment for hypertension, DM, and hypercholesterolaemia – would follow current national Ugandan guidelines [26]. The status quo would refer to the current health services environment where NCD treatment for PLWH is not delivered by HIV clinics.

According to the national guidelines [26], hypertension is defined as systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure (DBP) ≥90 mmHg; DM is defined as having blood test results for fasting blood glucose ≥7.0 mmol/L or random blood sugar ≥11.1mmol/L; and high total cholesterol is defined as total cholesterol ≥5.5mmol/L. In our analysis, we studied the cost-effectiveness of integrating screening and treatment for hypertension, DM, and hypercholesterolaemia, across sex and age groups of PLWH (Figure 1).

2.2 | Estimating the health benefits of integration

We built on Globorisk, a mathematical model that estimates the 10-year risk of CVD (stroke and IHD) for a given individual, based on age, sex and risk factors including SBP and DBP levels, DM status, smoking status and cholesterol level [27]. The Globorisk model was further augmented by Kintu and colleagues to assess the 10-year CVD risk among PLWH in Uganda [28]. Values for the model covariates (e.g. SBP, DPB levels) were drawn from a number of studies [21,29,30], which were conducted in Uganda or similar settings to reflect actual distributions of the risk factors and rates in the population. We then could estimate the 10-year CVD risk with and without integration intervention (Table 1). Age- and sex-based prevalence of risk factors in the population were sourced from nationally representative surveys (i.e. that used a randomly selected sample countrywide) including the national survey on NCDs (World Health Organization's STEPwise approach to Surveillance (STEPs) survey [21]). Statistics on HIV prevalence were obtained from Uganda's population-based HIV impact survey [20]. Further detail on the underlying Globorisk model developed is given in the Appendix S1 (section 1).

For the status quo, we assumed no change in the baseline distribution of risk factor profiles in the population [21], and hence of the subsequent 10-year CVD risk as estimated by Globorisk (i.e. projected CVD rates over 10 subsequent years based on past trends). For the integration impact on CVD, we drew from the published literature [19,31,32] to determine the net average proportional reduction in 10-year CVD risk, hence in the occurrence of both fatal and non-fatal CVD events (IHD, stroke) [10-15]. We used average treatment effects from the published literature [19,31,32] to assign changes in CVD risk per individual patient: treated individuals were assumed to all experience the same proportional reduction in CVD risk. For individuals with more than one risk factor, treatment effect was assumed to be multiplicative [19,29,33]. The subsequent 10-year CVD risks were then computed to estimate the number of CVD events with and without integration. In sum, the current adult Ugandan population (PLWH and non-PLWH) was followed over 10 subsequent years (e.g. 2017 to 2026), for which the cumulative CVD risks were estimated, in the case of integration intervention versus status quo.

2.3 | Estimating the costs of integration

We quantified the resources that would be required under both status quo and integration scenarios, along with their associated costs and prices of commodities and supplies,

Table 2. Parameter inputs and corresponding sources used in assessing the cost-effectiveness of HIV-NCD integration services in Uganda. Indicated in parentheses are uncertainty ranges.

Parameter	Estimate	Source
Demography		
Uganda population	38,607,200	United Nations [46]
HIV disease		
Prevalence among 15-49 year-olds (%)	6.0 (5.5-6.4)	HIV impact survey (2017) [20]
Proportion (%) of HIV-infected individuals enrolled in ART programs	64	Global AIDS update [47]
NCD risk factors		
Prevalence of hypertension (%)		STEPs survey (2014) [21] and Appendix S1 (section 1)
30-44 years	Men (24.5), Women (22.7),	
45-59 years	Men (32.9), Women (41.5),	
60-69 years	Men (35.3), Women (49.6)	
Prevalence of diabetes mellitus (%)		STEPs survey (2014) [21] and Appendix S1 (section 1)
30-44 years	Men (2.7), Women (1.9)	
45-59 years	Men (3.1), Women (4.2)	
60-69 years	Men (4.0) Women (5.8)	
Prevalence of high cholesterol levels (%)		STEPs survey (2014) [21] and Appendix S1 (section 1)
30-44 years	Men (5.1), Women (10.1)	
45-59 years	Men (8.3), Women (14.8)	
60-69 years	Men (7.3) Women (19.1)	
Coverage of NCD risk factor treatment		
Proportion currently on medication for hypertension (%)	7 (4 to 9)	STEPs survey (2014) [21]
Proportion currently on medication for diabetes mellitus (%)	1 (0 to 1)	
Proportion currently on medication for high cholesterol (%)	10 (6 to 14)	
Treatment efficacy for NCD risk factor		
Relative risk of stroke for hypertensive patients using single antihypertensive drugs	0.8 (0.7 to 0.9)	Turnbull et al. [32]
Relative risk of coronary events among diabetic patients with glycemic control	0.6 (0.6 to 0.7)	Stratton et al. [19]
Relative risk of coronary events among high cholesterol patients started on statin	0.7 (0.6 to 0.7)	LaRosa et al. [31]
Costs* (2017 USD, per specific type of care, per patient per year)		
Hypertension	$76 (32 to 144)	MoH Uganda [36]
Medical consultation	$2 (1 to 4)	
Laboratory and imaging tests (screening costs)	$33 (6 to 46)	
Medicines	$38 (24 to 90)	
Diabetes mellitus	$84 (22 to 143)	
Medical consultation	$2 (1 to 4)	
Laboratory and imaging tests (screening costs)	$5 (3 to 18)	
Medicines	$70 (17 to 109)	

Table 2. (*Continued*)

Parameter	Estimate	Source
High cholesterol	$97 (39 to 147)	
Medical consultation	$2 (1 to 4)	
Laboratory and imaging tests (screening costs)	$14 (7 to 20)	
Medicines	$79 (30 to 120)	
Fatal CVD event (< 30-day survival)	$610 (420 to 1220)	
Average cost of hospitalization	$100 (50 to 150)	
Treatment cost	$510 (370 to 1070)	
Non-Fatal CVD event (> 30-day survival)	$810 (494 to 1560)	
Average cost of hospitalization	$100 (50 to 150)	
Treatment cost during the acute phase	$510 (370 to 1070)	
Annual treatment cost for non-fatal CVD event	$200 (74 to 340)	
Cost of antiretroviral drugs	$265	Kimaro et al. (2017) [37]

ART = antiretroviral therapy; NCD = non-communicable disease; CVD = cardiovascular disease.
*Costs are based on Uganda's Ministry of Health (MoH) data and actual market prices for specific services in public facilities. These costs reflect the current Ugandan national guidelines for standards of care.

drawing from a set of previously outlined methodological principles [50].

We calculated the costs of managing risk factors and CVD events using an ingredients-based approach and took the provider perspective. We incorporated prices and costs of all resources required, importantly human resources, laboratory equipment, and drug costs. We conducted extensive consultations with local experts in Mbarara University Referral Hospital (clinicians and hospital managers), Makerere University (physicians and academicians), and the Ministry of Health (policymakers), to define the feasible modalities for integration under Uganda's existing health system. In the status quo, we assumed PLWH would receive risk factor treatment at levels similar to the general population (based on STEPs survey estimates [21]): 7% of PLWH with hypertension, 1% of PLWH with DM and 10% of PLWH with high cholesterol would receive treatment, respectively. Under integration, all PLWH receiving ART would be screened for risk factors and treated accordingly. Health workers' time devoted to accomplishing the additional tasks required (both screening and treatment tasks) were fully incorporated. Such human resources costs were calculated based on current government salary scales for civil servants [34]. We assumed each ART patient would be screened once, and patients identified with risk factors would then receive annual screenings and drug refills during routine ART visits. Time spent by each specific health cadre during patient visit was estimated through consultation with local experts; and average time spent by each cadre was multiplied to the mean hour wage rate (gross salary) per cadre to obtain mean human resources costs per visit. Imaging and diagnostic costs were based on recommended standard national guidelines for NCD management [26]. Through expert consultations, we determined the average cost for minimum laboratory investigations and imaging tests by taking the mean cost of services in specialized public facilities and primary health centres [26,35]. Drug costs were based on dosages from Uganda's 2017 to 2018 Medical Store Department price catalogue [36].

Cost of managing CVD events was also based on standard national guidelines. We computed average cost of laboratory investigations, imaging tests, drugs and hospitalization per CVD event. A non-fatal CVD event would receive additional drugs (as appropriate) and be clinically monitored annually. Monitoring of non-fatal CVD events would include laboratory and imaging tests. We also computed cost of ART for the averted fatal CVD cases drawing from recently published estimates [37]. We focused on ART costs for people with an averted fatal CVD case because averted non-fatal cases would still use ART without integration (in the status quo).

Lastly, for simplicity, our analysis excluded capital costs associated with infrastructure, buildings and other related facilities, under the assumption that those costs would remain covered by the already existing ART delivery services. All costs were estimated based on delivery by the Ugandan health system, and were discounted at 3% per year [40]. All prices were computed in local currency (UGS) and converted to 2017 USD using a mean exchange rate of USD 1 = UGS 3500 [38]. Table 2 provides a detailed description of all data inputs and corresponding sources; and additional information is provided in the Appendix S1 (section 2)

2.4 | CVD outcomes and cost-effectiveness of integration

As described above, 10-year CVD risks were obtained from Globorisk [27] and used to compute the number of CVD events (both fatal and non-fatal events), in the integration and status quo scenarios, respectively. Each CVD event was then converted into Years of Life Lost (YLL) due to premature death and Years Lived with Disability (YLD) by applying disability weights from the 2013 Global Burden of Disease study [39]. We used Ugandan life tables [46] and age-specific life expectancies to estimate YLLs associated with a premature CVD-related death and YLDs associated with a non-fatal CVD case, per five-year age group (e.g. 50 to 55 year-olds). CVD-risks were estimated over 10 years into the future; hence, we assumed that CVD events would occur at mid-time period (i.e.

year 5 into the future), and we estimated YLLs and YLDs for each five-year age group with respect to life expectancy for that age group forwarded five years into the future. Summing up YLLs and YLDs yielded disability-adjusted life years (DALYs) which were discounted at 3% per year, and the total number of DALYs corresponding to each scenario (integration vs. status quo).

Per scenario, we computed the total costs as the sum of the costs of treating individuals with hypertension, DM, and hypercholesterolaemia; and the costs of treating CVD cases (both fatal and non-fatal cases), and the ART costs. Incremental costs for integration were derived as the difference in total costs compared with status quo. We could then derive the net cost per DALY averted by integration.

2.5 | Sensitivity analyses

We pursued four univariate sensitivity analyses, where we varied one input parameter at a time independently while maintaining values for the other input parameters unchanged. First, we varied the costs to consider how changes in input prices might impact our findings and to allow for uncertainty behind our costing approach for NCD screening and treatment. Therefore, we tested higher and lower cost values for treating NCDs and CVDs to capture different levels of health system provision. The lower cost would represent a scenario where care is provided within primary care facilities with limited human resources and absence of chest X-rays, echocardiograms and electrocardiograms. The higher cost would represent a scenario where care is provided in specialized clinics with all recommended standards of care. Specifically, for treating hypertension, DM, and high cholesterol, the lower treatment cost was $32, 22 and 39 respectively; and the higher cost $144, 143 and 147 respectively. For treating CVD, the lower costs were $420 and 494 for fatal and non-fatal events, respectively; and the higher costs $1220 and 1560. Second, for the treatment effects, we used confidence intervals from the published literature [19,31,32] to examine scenarios where integration would have either minimal or maximal impact. Specifically, for the effect size of treatment for hypertension, DM, and high cholesterol, the higher estimates of effectiveness had relative risks of 0.70, 0.59 and 0.60 respectively; and the lower estimates relative risks of 0.91, 0.72 and 0.74. Third, we also studied possible reduced coverage, which would correspond to the situation of NCD care coverage being lower in specialized HIV clinics: we assumed that integration would only reach 75% of PLWH receiving ART (instead of 100% in the base case).

2.6 | Ethics approval

The study was approved by the ethical review boards of Mbarara University of Science and Technology (protocol number: 14/09-17), the Uganda National Council of Science and Technology, and the Harvard T.H. Chan School of Public Health (protocol number: IRB16-2062).

3 | RESULTS

Model outcomes were estimated for the current adult Ugandan population over 10 years of follow-up. Examining the 10-year CVD risk per age group and sex, we estimated a mean risk of 8.2% in 45-69 year-old PLWH women compared with 10.7% in 45-69 year-old PLWH men, in the status quo. This risk would decrease to 6.6% in women compared with

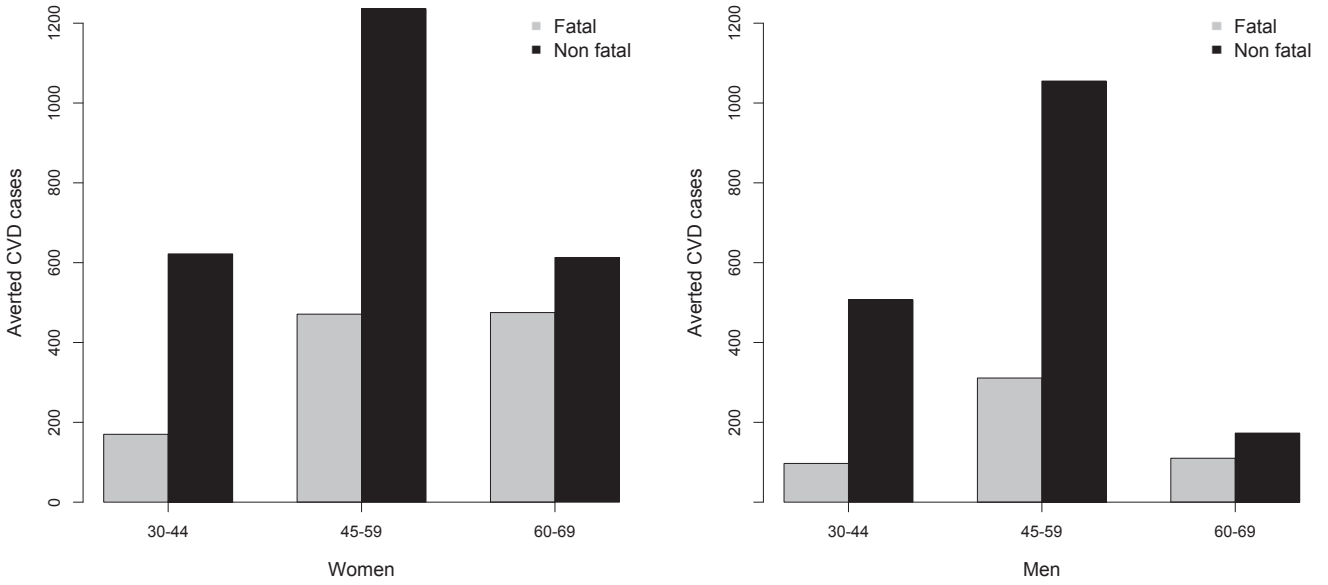

Figure 2. Averted cardiovascular disease (CVD) events (fatal and non-fatal events), over 10 years, among people living with HIV receiving antiretroviral therapy in Uganda, per age group (30 to 44, 45 to 59 and 60 to 69 year-olds) and sex, after integration.

Table 3. Averted cardiovascular disease (CVD) events, cost and net cost, and cost-effectiveness of NCD-HIV integration within HIV services in Uganda, disaggregated per age group (30-44, 45-59, 60-69 year-olds), and sex.

Age group (years)	Cost of adding NCD services	Additional ART Cost	Cost savings due to averted CVD Cases	Net cost	CVD cases averted	Deaths averted	DALYs averted	Net cost per DALY averted
Women								
30-44	$65,544,000	$887,000	$2,985,000	$63,446,000	790	170	7,210	8,800
45-59	$46,465,000	$1,934,000	$4,975,000	$43,424,000	1,705	470	13,350	3,255
60-69	$11,206,000	$1,375,000	$2,039,000	$10,541,000	1,090	475	7,305	1,445
Men								
30-44	$27,849,000	$470,000	$2,273,000	$26,046,000	605	95	4,705	5,535
45-59	$21,431,000	$1,240,000	$4,105,000	$18,566,000	1,365	310	9,700	1,915
60-69	$2,626,000	$301,000	$541,000	$2,386,000	285	110	1,700	1,400

Note: All costs are expressed in 2017 USD. DALY = disability-adjusted life year.

9.5% in men after integration (Appendix S1, Table S1). Consequently, with integration, the 10-year absolute CVD risk among 45 to 59 and 60 to 69 year-old women would decline by 19.6% (compared with the baseline absolute CVD risk) in overall CVD cases (corresponding to 1,705 and 1,090 cases, respectively). Comparatively, men would experience a 10.6% reduction (compared with baseline absolute CVD risk) in CVD cases among 45 to 59 and 60 to 69 year-olds (1,365 and 285 cases, respectively) (Figure 2). Integration of risk factor treatment would reach about 255,000 PLWH aged 30 to 69 years who are currently enrolled in ART programmes. It would prevent an estimated 5,840 CVD cases (14% of all CVD cases) from occurring in PLWH within the 10 years after integration.

Table 3 summarizes the number of CVD cases that would be averted, the costs of providing NCD screening and treatment, the cost savings due to averted CVD cases and the net cost per DALY averted, per age group and sex, with integration. Integration of services for hypertension, DM, and hypercholesterolaemia would have an incremental cost-effectiveness ranging from $8,800 to $1,400 per DALY averted, depending on the age and sex category. Targeting older age groups with higher CVD risks (e.g. 45 to 59 and 60 to 69 year-olds), among both women and men, would be more cost-effective. Overall, the incremental cost-effectiveness ratios are high when compared with common thresholds of $500 to 1000 per DALY (about one half and one time Uganda's gross domestic product (GDP) per capita).

3.1 | Sensitivity analyses

Table 4 displays the impact of the univariate sensitivity analyses on the cost-effectiveness estimates (in net cost per DALY averted). Over the varying range of input parameters tested, the major changes observed followed the use of lower costs for treating hypertension, DM, and high cholesterol: for example the net cost per DALY averted in 60 to 69 year-olds would then decrease to $540 and $505 in women and men, respectively. Likewise, cost-effectiveness would be enhanced (net cost per DALY averted decreased) with higher treatment effectiveness estimates, and with higher cost estimates for CVD treatment.

4 | DISCUSSION

We pursued a cost-effectiveness analysis of integrating NCD treatment among PLWH receiving ART in Uganda: we quantified the potential health gains, costs and cost-effectiveness of integrating screening and treatment for hypertension, DM and high cholesterol in HIV services in Uganda. We developed a cost-epidemiological model drawing from nationally representative surveys, the published literature, and Ugandan national guidelines. Our analysis is one of a few studies to date that have proposed an economic evaluation of integrating NCD care into HIV services in a low- and middle-income sub-Saharan African country [23,24].

We found that NCD integration into existing ART clinics in Uganda would be associated with a decrease in the 10-year CVD risk in PLWH. This is consistent with previous findings on the impact of NCD treatment on CVD incidence: for example, Ortegon and colleagues pointed that treating risk factors was associated with a decline in individual CVD risk directly proportional to the baseline risk level [41]. We also estimated a wide range in cost-effectiveness, improving with targeting older age groups, from about $1,400 to 8,800 per DALY averted. The most cost-effective scenario (around $1,400 per DALY averted) would correspond to targeting the oldest age group (60 to 69 year-olds). Yet, given that life expectancy at birth is about 63 years and that the 60 to 69 year-olds living with HIV represent a small population in Uganda [46], targeting all adults beyond age 45 would seem more appropriate. Our estimate ranges are comparable with previous cost-effectiveness findings for low- and middle-income countries (LMICs) recently reported by the *Disease Control Priorities* third edition, where Horton and colleagues [42] ranked different health interventions for LMIC settings showing large variations in net cost per DALY averted. For example, prevention of mother to child transmission of HIV and secondary treatment of CVD would cost $100 to $1000 per DALY averted; whereas, strategies for primary prevention of CVD would cost $1000 to $10,000 per DALY [42]. Our findings fall within the higher range of $500 to 1000 per DALY thresholds (around one half or one time Uganda's GDP per capita) commonly reported [42]; and our estimates for younger age groups (e.g.

Table 4. Results from selected univariate sensitivity analyses on costs, treatment effects, and coverage inputs for NCD-HIV integration in Uganda among people living with HIV receiving antiretroviral therapy, disaggregated per age group (30-44, 45-59, 60-69 year-olds), and sex.

	Age group (years)	Cost of adding NCD services	Additional cost of ART	Cost savings due to averted CVD events	Net cost	DALYs averted	Net cost per DALY averted
Lower estimates for cost of treating hypertension, diabetes mellitus, and high cholesterol							
Women	30-44	27,901,000	887,000	2,985,000	25,803,000	7210	3580
	45-59	19,312,000	1,934,000	4,975,000	16,271,000	13350	1220
	60-69	4,614,000	1,375,000	2,039,000	3,949,000	7305	540
Men	30-44	11,842,000	470,000	2,273,000	10,040,000	4705	2135
	45-59	9,023,000	1,240,000	4,105,000	6,158,000	9700	635
	60-69	1,098,000	301,000	541,000	858,000	1700	505
Higher estimates for cost of treating hypertension, diabetes mellitus, and high cholesterol							
Women	30-44	113,590,000	887,000	2,985,000	111,492,000	7210	15460
	45-59	81,713,000	1,934,000	4,975,000	78,672,000	13350	5895
	60-69	19,666,000	1,375,000	2,039,000	19,001,000	7305	2600
Men	30-44	49,520,000	470,000	2,273,000	47,718,000	4705	10140
	45-59	38,066,000	1,240,000	4,105,000	35,202,000	9700	3630
	60-69	4,691,000	301,000	541,000	4,451,000	1700	2615
Lower estimate for cost of treating cardiovascular disease							
Women	30-44	65,544,000	887,000	1,241,000	65,190,000	7210	9040
	45-59	46,465,000	1,934,000	2,136,000	46,264,000	13350	3465
	60-69	11,206,000	1,375,000	942,000	11,638,000	7305	1595
Men	30-44	27,849,000	470,000	945,000	27,374,000	4705	5815
	45-59	21,431,000	1,240,000	1,755,000	20,917,000	9700	2155
	60-69	2,626,000	301,000	249,000	2,678,000	1700	1575
Higher estimate for cost of treating cardiovascular disease							
Women	30-44	65,544,000	887,000	5,203,000	61,228,000	7210	8490
	45-59	46,465,000	1,934,000	8,736,000	39,664,000	13350	2970
	60-69	11,206,000	1,375,000	3,644,000	8,937,000	7305	1225
Men	30-44	27,849,000	470,000	3,962,000	24,357,000	4705	5175
	45-59	21,431,000	1,240,000	7,200,000	15,471,000	9700	1595
	60-69	2,626,000	301,000	966,000	1,961,000	1700	1150
Higher estimates for NCD risk factor treatment effectiveness							
Women	30-44	65,544,000	1,751,000	5,961,000	61,333,000	14325	4280
	45-59	46,465,000	3,223,000	8,598,000	41,091,000	22640	1815
	60-69	11,206,000	2,048,000	3,149,000	10,104,000	11015	915
Men	30-44	27,849,000	1,190,000	5,860,000	23,179,000	12055	1925
	45-59	21,431,000	2,863,000	10,178,000	14,116,000	23290	605
	60-69	2,626,000	629,000	1,224,000	2,031,000	3660	555
Lower estimates for NCD risk factor treatment effectiveness							
Women	30-44	65,544,000	564,000	1,872,000	64,236,000	4550	14120
	45-59	46,465,000	1,064,000	2,531,000	44,998,000	7080	6355
	60-69	11,206,000	568,000	709,000	11,065,000	2860	3865
Men	30-44	27,849,000	114,000	499,000	27,464,000	1075	25580
	45-59	21,431,000	672,000	1,981,000	20,122,000	4945	4065
	60-69	2,626,000	181,000	290,000	2,517,000	980	2560
NCD risk factor treatment coverage reduced to 75%							
Women	30-44	47,848,000	665,000	2,239,000	46,275,000	5410	8555
	45-59	33,937,000	1,450,000	3,732,000	31,656,000	10010	3160
	60-69	8,148,000	1,031,000	1,529,000	7,650,000	5480	1395

Table 4. (*Continued*)

	Age group (years)	Cost of adding NCD services	Additional cost of ART	Cost savings due to averted CVD events	Net cost	DALYs averted	Net cost per DALY averted
Men	30-44	20,382,000	353,000	1,705,000	19,031,000	3530	5390
	45-59	15,669,000	930,000	3,079,000	13,520,000	7275	1860
	60-69	1,921,000	226,000	406,000	1,741,000	1275	1365

Note: All costs are expressed in 2017 USD. NCD = non-communicable disease. CVD = cardiovascular disease (stroke and ischemic heart disease). DALY = disability-adjusted life year.

30 to 44 year-olds) exceed such thresholds. In sum, in our modelling, the impact of NCD screening and treatment among PLWH would yield a modest CVD risk reduction (<1% in absolute risk reduction) at very high costs.

A series of articles have reviewed five potential modalities for NCD-HIV integration in LMICs [7,22-23,25]. Among them, only two modalities embraced a comprehensive care approach for NCDs, and emphasized providing combined screening and treatment services at the same delivery point. These two modalities would leverage on the existing HIV infrastructure to incorporate NCD services and to convert HIV clinics to serve patients with other chronic diseases who are not necessarily HIV-positive. The already established strong health system for HIV services would have capacity to be augmented towards a "chronic care model." Considering the limited funding for NCDs and the fragmentation of health systems in many developing countries, it may be most practical to begin NCD services provision with patients currently engaged in ART before expanding to others outside the scope of HIV programmes [1,22]. In 2016/17, Ugandan national health expenditure on HIV/AIDS amounted to US$692 million [48] (out of an estimated $1.7 billion of total health expenditure [49]). The NCD-HIV integration proposed here would present net costs of about $16 million (when targeting all PLWH receiving ART above age 30), which corresponds to roughly 2.4% of HIV/AIDS expenditure and 1.0% of total health expenditure.

Findings from our analysis could be used as inputs to NCD-HIV integration policy design in Uganda. However, additional evidence would be required to support policy change. First, targeting NCD care to a specific population subgroup raises fundamental ethical dilemmas. Integrating NCD care to HIV services would demand careful examination of fairness principles underlying the decision to potentially deny such care to those not infected with HIV yet suffering NCDs. However, health systems in SSA have experience in formulating policy under such dilemmas, as in the case of integrating cervical cancer screening into HIV services [43], where higher risk of cervical cancer among HIV-infected women was among several motivations [44,45]. Second, leveraging on the already existing HIV infrastructure to introduce NCD care is likely to be less costly and has the potential to build health system capacity to address the growing NCD epidemic in the general population. Yet, further evidence on the impact of integration on patient waiting time, retention and potentially overburdening health workforce would be necessary.

Our analysis presents a number of important limitations. First, we limited our outcomes to health gains and a provider perspective: thus, we excluded non-health benefits such as increased work productivity, and other indirect costs such as travel costs and time losses, which could be averted with prevention of CVD events. Second, we assumed similar treatment effectiveness and impacts would apply across all PLWH patients, and did not account for patient heterogeneity. We also used effectiveness estimates from studies conducted in high-income countries, due to lack of data available in LMICs, whereas sensitivity analyses with additional treatment effectiveness estimates [30] and drug adherence considerations could be conducted. Likewise, supply chain systems that are weak in LMICs like Uganda and that can lead to delays and stockouts in drug delivery would likely diminish integration impact. In addition, due to lack of data, the model did not account for changes in other conditions which could be prevented by controlling NCDs such as retinopathy, renal diseases, and amputations; neither did we incorporate long-standing NCDs with morbidity among older individuals, which could well reduce the health benefits (e.g. healthy life years) among the targeted older age groups. Another limitation pertains to the use of the Globorisk prediction model, which was developed using cohorts of non-African populations [27]. Although we could not validate Globorisk to our Ugandan population, we recalibrated it by updating age- and sex-specific CVD rates and risk factor prevalence using the nationally representative STEPs survey [21,28]. Third, our cost estimates might not be nationally representative for Uganda, and our costs for screening and treatment were assumed to remain constant over 10 years, without consideration of changes in technology and evolution in drug prices over time. We considered the full costs implied by the national guidelines of standards of care (e.g. use of X-rays and electrocardiograms) which may not be currently implementable in Uganda. And, we did not account for impact of scale on the cost of delivery (e.g. marginal cost decreasing with increasing volume of patients). However, to test the impact of our assumptions, we conducted a number of univariate sensitivity analyses (Table 4). Fourth, we did not consider NCD care provision among private facilities. Yet, public facilities account for the large majority of facilities delivering ART in Uganda, and NCD-HIV integration via private facilities is largely left for future work. Also, adding risk factor treatment could be associated with longer clinical visits and waiting times, demanding additional capital costs to expand facilities. We however did not incorporate the possibility for longer waiting times associated with increased time taken to jointly provide HIV/NCD care, which could raise the additional capital costs needed to expand facilities and require more

Box 1. Policy implications

- Integrating screening and treatment of NCDs into HIV care and treatment in Uganda could yield important health and financial benefits.
- Integrating screening and treatment for hypertension, high cholesterol, and diabetes mellitus among older PLWH in Uganda would present value for money comparable to other proposed interventions to address NCDs in low- and middle-income countries.

Box 2. Research implications

- Economic evaluation research should be conducted on assessing the value for money of screening schedules for common NCDs in PLWH versus the whole population; and on expanding HIV care and treatment delivery toward a chronic disease care clinic model.
- Health services research should be conducted on the economies of scope and economies of scale along with the system requirements including human resources implications when integrating NCD services within HIV care and treatment delivery in sub-Saharan Africa.

health workforce, especially in the context of already financially constrained HIV delivery systems. Lastly, for simplicity, we made several assumptions on integration coverage: PLWH receiving ART would be screened and treated; and the proportion of enrolled PLWH would remain constant at 64% (e.g. ART coverage in Uganda) over 10 subsequent years, even though, based on the current 90-90-90 goal (test 90% of PLWH, initiate 90% of PLWH on ART and attain viral suppression to 90% of PLWH on ART), expansion of ART would be expected in the coming years in Uganda.

5 | CONCLUSIONS

As a conclusion, this paper offers preliminary evidence on the cost-effectiveness of integration of screening and treatment services for hypertension, DM and high cholesterol in PLWH in Uganda and SSA (Box 1). Such approach could potentially be replicated to other sub-Saharan African countries with similar CVD risk profiles and treatment costs for NCDs, drawing from local NCD prevalence data which may contrast with Uganda. Such integration could improve survival of PLWH and decrease the burden of disease in SSA. Yet, further research on the ethics, other costs and sustainability of NCD integration and chronic care models will be required to support the conversion of current health systems in low-income countries towards addressing the rapidly expanding NCD epidemic (Box 2).

COMPETING INTERESTS

We declare no competing interests.

AUTHORS' AFFILIATIONS

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AUTHORS' CONTRIBUTIONS

SV conceived the study. DS built the model, analyzed data, prepared results and wrote the first draft of the manuscript. AK, DG, GM, SB, SO, WM and PCK provided data and advice for the analysis. NAM and GD reviewed and provided advice on the simulation methods. All authors contributed to writing and reviewing the manuscript. SV had final responsibility for submitting to publication.

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SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article.

Appendix S1. Supplementary appendix.

Table S1. Estimated cumulative 10-year cardiovascular disease (CVD) risk (expressed in percent) among people living with HIV in Uganda, per age group (30 to 44, 45 to 59, or 60 to 69 year-olds) and sex, with either current status quo or with integrating non-communicable disease risk factor treatment among people living with HIV receiving antiretroviral therapy.

Table S2. Detailed description of the cost inputs used in the cost-effectiveness model of NCD-HIV integration in Uganda.

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RESEARCH ARTICLE

Statins for atherosclerotic cardiovascular disease prevention in people living with HIV in Thailand: a cost-effectiveness analysis

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Abstract

Introduction: People living with HIV (PLHIV) have an elevated risk of atherosclerotic cardiovascular disease (CVD) compared to their HIV-negative peers. Expanding statin use may help alleviate this burden. However, the choice of statin in the context of antiretroviral therapy is challenging. Pravastatin and pitavastatin improve cholesterol levels in PLHIV without interacting substantially with antiretroviral therapy. They are also more expensive than most statins. We evaluated the cost-effectiveness of pravastatin and pitavastatin for the primary prevention of CVD among PLHIV in Thailand who are not currently using lipid-lowering therapy.

Methods: We developed a discrete-state microsimulation model that randomly selected (with replacement) individuals from the TREAT Asia HIV Observational Database cohort who were aged 40 to 75 years, receiving antiretroviral therapy in Thailand, and not using lipid-lowering therapy. The model simulated each individual's probability of experiencing CVD. We evaluated: (1) treating no one with statins; (2) treating everyone with pravastatin 20mg/day (drug cost 7568 Thai Baht ($US243)/year) and (3) treating everyone with pitavastatin 2 mg/day (drug cost 8182 Baht ($US263)/year). Direct medical costs and quality-adjusted life-years (QALYs) were assigned in annual cycles over a 20-year time horizon and discounted at 3% per year. We assumed the Thai healthcare sector perspective.

Results: Pravastatin was estimated to be less effective and less cost-effective than pitavastatin and was therefore dominated (extended) by pitavastatin. Patients receiving pitavastatin accumulated 0.042 additional QALYs compared with those not using a statin, at an extra cost of 96,442 Baht ($US3095), giving an incremental cost-effectiveness ratio of 2,300,000 Baht ($US73,812)/QALY gained. These findings were sensitive to statin costs and statin efficacy, pill burden, and targeting of PLHIV based on CVD risk. At a willingness-to-pay threshold of 160,000 Baht ($US5135)/QALY gained, we estimated that pravastatin would become cost-effective at an annual cost of 415 Baht ($US13.30)/year and pitavastatin would become cost-effective at an annual cost of 600 Baht ($US19.30)/year.

Conclusions: Neither pravastatin nor pitavastatin were projected to be cost-effective for the primary prevention of CVD among PLHIV in Thailand who are not currently using lipid-lowering therapy. We do not recommend expanding current use of these drugs among PLHIV in Thailand without substantial price reduction.

Keywords: HIV; cardiovascular disease; statin; cost-effectiveness; Thailand; antiretroviral therapy

Additional information may be found under the Supporting Information tab for this article.

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1 | INTRODUCTION

People living with HIV (PLHIV) have an elevated risk of atherosclerotic cardiovascular disease (CVD) compared to their HIV-negative peers [1]. This is only partially explained by the high prevalence of cardiovascular risk factors among PLHIV. In a landmark study of 82,459 US veterans, those who were HIV-positive had a 48% increased risk of incident myocardial infarction (MI) compared with HIV-negative participants, even after adjusting for well-known risk factors, comorbidities and substance use [2]. Similar studies have also found a small, but significant increase in ischaemic stroke incidence associated with HIV infection [3–5].

The increased CVD risk associated with HIV may be mediated by the virus itself, past or present immunodeficiency, adverse effects of antiretroviral therapy (ART), deficiencies in

cardiovascular care in PLHIV, or a combination of these factors [6]. As ART is often initiated at an advanced stage of HIV in low- and middle-income countries [7] and untreated HIV is associated with an increased risk of CVD [8], it is possible that the risk is further exacerbated in settings where resources are limited [9,10].

Statins reduce atherosclerotic CVD risk primarily by lowering LDL cholesterol levels [11]. They also have anti-inflammatory properties that may enhance their effectiveness in PLHIV [12]. In a recent survey of HIV clinics in low- and middle-income Asian countries (including Thailand), 94% reported that patients could access statins through the clinic or the same facility as the clinic [13]. Current Thai guidelines recommend lipid-lowering therapy be initiated among PLHIV with a 10-year risk of CVD greater than 10%, consistent with general population guidelines [14]. However, studies among the general population in Thailand and other middle-income countries suggest statin use could be cost-effective for those at lower risk of CVD [15–17]. It is uncertain whether this is likely to extend to PLHIV, despite the elevated risk of CVD associated with HIV infection, as statin use in the context of ART is complicated by the risk of drug interactions leading to intolerance or reduced efficacy. With concomitant protease inhibitor use, simvastatin and lovastatin are contraindicated, whereas atorvastatin and rosuvastatin require modified dosing [18]. With concomitant efavirenz or etravirine use, statins may require dose modification [18].

Pravastatin and pitavastatin are preferred agents among PLHIV because they improve cholesterol levels and reduce immune activation without interacting substantially with ART [19–22]. Although generic pravastatin formulations are available, they tend to be more expensive than other generic statin formulations. Pitavastatin is a newer statin and in many settings is more expensive than pravastatin, however, current evidence suggests it produces greater improvements in cholesterol levels than pravastatin among PLHIV [19].

Given these trade-offs, we evaluated the cost-effectiveness of pravastatin and pitavastatin for the primary prevention of CVD among PLHIV in Thailand who are not currently using lipid-lowering therapy. We believe this is the first study to assess the cost-effectiveness of expanded statin use among PLHIV in Thailand.

2 | METHODS

2.1 | Study population

We used individual patient data from all Thai sites contributing to the TREAT Asia HIV Observational Database (TAHOD), the updated Data collection on Adverse Effects of Anti-HIV Drugs (D:A:D) CVD risk equation, and published literature to estimate medical costs and quality-adjusted life-years (QALYs) among adult PLHIV in Thailand. TAHOD is an ongoing collaboration of 21 HIV clinics in the Asia-Pacific region that is part of the International epidemiology Databases to Evaluate AIDS Asia-Pacific [23]. Participating clinics follow local guidelines and regulations regarding patient consent and ethics review. Our study population included patients enrolled in TAHOD at one of the four Thai sites involved (Ramathibodi Hospital, Bangkok; HIV-NAT Research Collaboration/Thai Red Cross AIDS Research Centre, Bangkok; Research Institute for Health Sciences, Chiang Mai; and Chiangrai Prachanukroh Hospital, Chiang Rai) who had documentation of at least one clinic visit on or after 1 January 2013 and who, at their last documented clinic visit, were aged 40 to 75 years, had no history of CVD, were not using lipid-lowering therapy, had been using ART for at least six months, and had a CD4 cell count> 100 cells/mm^3. Stable ART was included as a selection criterion as this should be prioritized by PLHIV over CVD risk management. Table 1 further characterizes the 917 PLHIV included in our study population.

2.2 | Model structure

We developed a discrete-state microsimulation model that randomly selected (with replacement) 10,000 patients from our study population and simulated their experience over time. The model assumed the Thai healthcare sector perspective and applied a 20-year time horizon. Patients started in the healthy state and were at risk of coronary intervention without an MI, MI, ischaemic stroke, haemorrhagic stroke, cardiovascular death or non-CVD death. Coronary interventions included coronary artery bypass graft (CABG) and

Table 1. Study population characteristics at beginning of simulation

Characteristic		N = 917
Sex	Male	442 (48.2)
Age, years	Median (IQR)	48.6 (44.6, 54.6)
Mode of HIV exposure	Heterosexual	840 (91.6)
	Homosexual	53 (5.8)
	Intravenous drug use	13 (1.4)
	Other	11 (1.2)
Hepatitis C antibody status	Positive	55 (6.0)
Hepatitis B surface antigen status	Positive	90 (9.8)
Family history of CVD	Yes	84 (9.2)
Diabetic	Yes	60 (6.5)
Current smoker	Yes	133 (14.5)
Ever smoked	Yes	327 (35.7)
Systolic blood pressure, mmHg	Median (IQR)	124 (115, 135)
Using antihypertensive medication	Yes	105 (11.5)
Total cholesterol, mmol/L	Median (IQR)	5.0 (4.3, 5.6)
HDL cholesterol, mmol/L	Median (IQR)	1.3 (1.1, 1.6)
LDL cholesterol, mmol/L	Median (IQR)	3.3 (2.7, 3.9)
CD4 cell count, cells/mm^3	Median (IQR)	555 (419, 712)
D:A:D risk score, 5-year risk of CVD	≤1%	227 (24.8)
	>1% to 5%	556 (60.6)
	>5%	134 (14.6)

All values are n (%N) unless otherwise specified. CVD, cardiovascular disease; IQR, interquartile range; D:A:D, data collection on Adverse Effects of Anti-HIV Drugs study.

Table 2. Key model parameters

Parameter	Base case (range for sensitivity)	Source
Probabilities		
CVD risk factors		
Probability of CVD event (D:A:D equation)	Varies by individual[a]	[24]
Annual probability of developing diabetes	Varies by age and sex[b]	[25]
Annual probability of smoking cessation[c]	Varies by age[b]	[26]
Increase in systolic blood pressure per year of age	Varies by age and sex[b]	[27]
Myocardial Infarction		
Probability of CVD event being fatal/non-fatal MI	0.488 (0.450 to 0.520)	[24]
Probability of CABG after MI[c]	0.031 (0.024 to 0.039)	[28]
Probability of PCI after MI[c]	0.288 (0.268 to 0.308)	[28]
Probability of MI being fatal[c]	0.177 (0.161 to 0.195)	[28]
Stroke		
Probability of CVD event being fatal/non-fatal stroke	0.292 (0.250 to 0.320)	[24]
Probability of stroke being ischemic[c]	0.693 (0.690 to 0.700)	[29]
Probability of ischemic stroke being fatal[c]	0.284 (0.236 to 0.335)	[30]
Probability of hemorrhagic stroke being fatal[c]	0.484 (0.358 to 0.613)	[30]
CVD intervention (without prior MI/stroke)		
Probability of CVD event being an intervention	0.163 (0.140 to 0.190)	[24]
Probability of intervention being CABG[c]	0.241 (0.185 to 0.303)	[28]
Probability of intervention being PCI[c]	0.759 (0.697 to 0.815)	[28]
Probability of MI after CABG[c]	0.100 (0.050 to 0.300)	[31]
Probability of MI after PCI[c]	0.041 (0.036 to 0.048)	[32]
Death		
Probability of CVD event being other CVD death	0.044 (0.030 to 0.060)	[24]
Hazard of other CVD death for past MI/stroke vs no past MI/stroke	2.000 (1.000 to 3.000)	Assumption
Probability of non-CVD death	Varies by age, sex and CD4[d]	[33]
Recurrent events		
Probability of recurrent MI[c]	Varies by age, sex and time since last MI[d]	[34,35]
Probability of CABG after recurrent MI[c]	0.031 (0.024 to 0.039)	[28]
Probability of PCI after recurrent MI[c]	0.288 (0.268 to 0.308)	[28]
Probability that recurrent MI is fatal[c]	0.217 (0.109 to 0.364)	[36]
Probability of recurrent ischemic stroke[c]	Varies by time since last stroke[d]	[30,37–39]
Probability that recurrent ischemic stroke is fatal[c]	0.270 (0.140 to 0.420)	[37]
Probability of recurrent hemorrhagic stroke in first year after initial[c]	0.057 (0.015 to 0.409)	[37]
Probability of recurrent hemorrhagic stroke in subsequent years[c]	Varies by individual[e]	[37]
Probability that recurrent hemorrhagic stroke is fatal[c]	0.430 (0.070 to 0.930)	[37]
Probability of ischemic stroke after MI[c]	Varies by gender and time since MI[d]	[37–40]
Probability that ischemic stroke after MI is fatal[c]	0.270 (0.140 to 0.420)[f]	Assumption
Probability of MI after stroke[c]	Varies by age, gender and time since stroke[d]	[35,38,41]
Probability that MI after stroke is fatal[c]	0.217 (0.109 to 0.364)[g]	Assumption
Probability of hemorrhagic stroke after MI	Varies by individual[e]	Assumption
Probability of hemorrhagic stroke after ischemic stroke	Varies by individual[e]	Assumption
Probability of hemorrhagic stroke after MI or ischemic stroke being fatal[c]	0.484 (0.358 to 0.613)[h]	Assumption
Efficacy and safety of pravastatin and pitavastatin		
Reduction in total cholesterol associated with pravastatin 20 mg, %	13.7 (2.2 to 25.2)	[19]
Reduction in total cholesterol associated with pitavastatin 2 mg, %	19.1 (6.9 to 31.3)	[19]
Increase in HDL cholesterol associated with pravastatin 20 mg, %	7.2 (0.0 to 22.6)	[19]
Increase in HDL cholesterol associated with pitavastatin 2 mg, %	8.9 (0.0 to 26.4)	[19]
Additional reduction in CVD risk associated with statin use (i.e. due to factors other than lipid change), %	0.0 (0.0 to 30.0)	Assumption
Hazard ratio of hemorrhagic stroke for statin use vs no statin[c]	1.0001 (1.0000 to 1.0002)	[11]
Costs, 2018 Thai Baht		

Table 2. (*Continued*)

Parameter	Base case (range for sensitivity)	Source
HIV management	59,856 (29,929 to 89,784)	[42,43]
Non-fatal MI medical management[c]	35,441 (17,721 to 53,162)	[44]
PCI[c]	215,765 (107,882 to 323,647)	[44]
CABG[c]	316,475 (158,238 to 474,714)	[44]
Non-fatal MI management – first year post-MI[c]	62,245 (34,974 to 143,252)	[45]
Non-fatal MI management – after first year post-MI[c]	17,780 (8890 to 26,670)	[45]
Fatal MI[c]	221,915 (81,878 to 356,072)	[45]
Non-fatal ischemic stroke hospitalization[c]	26,668 (23,497 to 29,820)	[17,46]
Non-fatal ischemic stroke management – first year post-stroke[c]	42,435 (39,284 to 45,587)	[17,46]
Non-fatal ischemic stroke management – after first year post-stroke[c]	10,932 (8746 to 13,119)	[17]
Fatal ischemic stroke[c]	54,671 (43,737 to 65,606)	[17]
Non-fatal hemorrhagic stroke hospitalization[c]	26,668 (23,497 to 29,820)[i]	Assumption
Non-fatal hemorrhagic stroke management – first year post-stroke[c]	42,435 (39,284 to 45,587)[i]	Assumption
Non-fatal hemorrhagic stroke management – after first year post-stroke[c]	10,932 (8746 to 13,119)[i]	Assumption
Fatal hemorrhagic stroke[c]	54,671 (43,737 to 65,606)[i]	Assumption
Other cardiovascular death[c]	221,915 (81,878 to 356,072)[j]	Assumption
Statin-associated diabetes, average cost/individual taking statin/year[c]	2.30 (1.70 to 3.70)	[47,48]
Statin-associated myopathy, average cost/individual taking statin/year[c]	0.05 (0.02 to 0.08)	[49,50]
Pravastatin 20 mg, 12-month supply	7568 (3784 to 11,352)	[51]
Pitavastatin 2 mg, 12-month supply	8182 (4091 to 12,273)	[51]
Blood lipid test	660 (495 to 825)	[15]
Utilities		
Weights		
No history of CVD	1.0000	Assumption
History of MI[c]	0.9510 (0.9280 to 0.9690)	[52]
History of ischemic stroke[c]	0.6840 (0.5630 to 0.7940)	[52]
History of hemorrhagic stroke[c]	0.6840 (0.5630 to 0.7940)	[52]
History of MI and ischemic stroke[c]	0.6505 (0.5225 to 0.7694)	[52]
History of MI and hemorrhagic stroke[c]	0.6505 (0.5225 to 0.7694)	[52]
Quality-of-life decrements		
PCI[c]	0.0061 (0.0040 to 0.0087)	[52]
CABG[c]	0.0128 (0.0084 to 0.0184)	[52]
Acute MI[c]	0.0076 (0.0051 to 0.0106)	[52]
Acute ischemic stroke[c]	0.0242 (0.0158 to 0.0335)	[52]
Acute hemorrhagic stroke[c]	0.0242 (0.0158 to 0.0335)	[52]
Diabetes, average toll/individual taking statin/year[c]	0.00005 (0.00003 to 0.00007)	[47,52]
Myopathy, average toll/individual taking statin/year[c]	0.0000010 (0.0000007 to 0.0000012)	[49,52]
Daily statin administration/pill burden[c]	0.00000 (0.00000 to 0.00384)	[53]
Discounting and time horizon		
Annual discount rate (applied to costs and benefits)	0.03 (0.00 to 0.05)	[54]
Time horizon, years	20 (10 to 30)	[54]

[a]D:A:D equation uses age, sex, diabetes status, family history of CVD, current and past smoking status, total cholesterol, HDL cholesterol, systolic blood pressure, and CD4 cell count to calculate CVD risk; [b]see Tables S1, S2, S3; [c]based on general population or high-income setting; [d]see Figures S2, S3, S4, S5, S6; [e]same as probability of incident hemorrhagesame as probability of incident hemorrhagic stroke calculated with D:A:D equation.ic stroke calculated with D:A:D equation;; [f]same as probability of recurrent ischemic stroke being fatal; [g]same as probability of incident hemorrhagic stroke calculated with D:A:D equation; [h]same as probability of incident hemorrhagic stroke being fatal; [i]as for ischemic stroke hospitalization/management; [j]as for fatal MI. CVD, cardiovascular disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; MI, myocardial infarction.

percutaneous coronary intervention (PCI). Further detail is provided in the Supplementary Material, including Figure S1 which presents a schematic of the core model structure. Key model parameters are detailed in Table 2.

At the start of each annual cycle, the model estimated an individual's probability of transitioning from the healthy state to one of the CVD states based on their D:A:D CVD risk score [24,55]. The D:A:D equation is the only well-validated

HIV-specific CVD risk equation and is recommended for PLHIV by the American Heart Association [56]. It has been shown to produce similar estimates to the Ramathibodi-Electricity Generating Authority of Thailand (Rama-EGAT) CVD risk equation [57] among PLHIV in Thailand [58]. We used the reduced D:A:D CVD risk equation (which is based on patient age, sex, diabetes status, family history of CVD, current smoking status, past smoking status, total cholesterol, HDL cholesterol, systolic blood pressure and CD4 count) rather than the full equation (which also includes ART) because the reduced model is recommended for patients exposed to ART for more than five years [24]. Individual CVD risk scores were calculated using patient data, adding one year of age for each cycle, assuming age- and sex-specific changes in systolic blood pressure [27] and rates of diabetes [25], and age-specific rates of smoking cessation [26]. All other variables used to calculate CVD risk were kept constant over time.

As the D:A:D risk score calculates five-year probability of CVD, we converted scores to rates, divided them by five and converted to one-year probabilities. Since the risk score defines CVD as a composite of coronary intervention, MI, stroke (ischaemic or haemorrhagic) or other cardiovascular death, we apportioned the calculated risk into individual event types based on the proportions reported in Friis-Moller *et al.* [24] Each individuals risk of non-CVD death was estimated by subtracting their calculated risk of CVD death from their age, sex and CD4 count specific risk of all-cause mortality [33]. Recurrent event probabilities (for example, the probability of a second MI or the probability of an MI after a prior ischaemic stroke) were mainly based on published estimates for the general population in high-income countries due to a lack of HIV-specific data or data from low- and middle-income countries; we did not use the D:A:D CVD risk score or a HIV-specific hazard ratio as current evidence suggests that risk factors for primary CVD differ substantially from those of recurrent CVD [34,59–61]. Individuals accumulated costs and benefits up until their death or the time horizon, whichever came first.

2.3 | Treatment strategies

We evaluated three treatment strategies in our base-case analysis: (1) treating none of the study population with a statin; (2) treating the entire study population with pravastatin 20 mg/day and (3) treating the entire study population with pitavastatin 2 mg/day. We assumed patients using pravastatin and pitavastatin would exhibit sufficient adherence to achieve the same improvements in total cholesterol and HDL cholesterol observed in a recent clinical trial among PLHIV [19]. This trial, which primarily recruited participants of non-Asian ethnicity, used doses of 40 mg/day for pravastatin and 4 mg/day for pitavastatin. However, we assumed lower doses would achieve similar efficacy in Asian patients, as has been shown for other statins [62]. Total and HDL cholesterol improvements were used to quantify efficacy, despite statins primarily reducing CVD risk via lowering LDL cholesterol, because these are the cholesterol variables included in the D:A:D CVD risk equation. In our base-case analysis, we assumed pravastatin would reduce total cholesterol by 13.7% and increase HDL cholesterol by 7.2%, whereas pitavastatin would reduce total cholesterol by 19.1% and increase HDL cholesterol by 8.9% [19]. We assumed statin therapy only reduced CVD risk by improving cholesterol levels. However, in sensitivity analyses, we assumed additional CVD preventative efficacy to account for the possibility that the anti-inflammatory properties of statins may provide additional benefit among PLHIV [12].

We did not assume statins prevent any non-CVD outcomes as the current literature on this topic is inconclusive [63]. Since statins have been associated with an increased risk of haemorrhagic stroke [11], diabetes [47] and myopathy [49], we assumed hazard ratios and costs for these adverse events consistent with literature from the general population (see Table 2). Current evidence suggests there is little difference between statin types in terms of their adverse event profile [64].

2.4 | Cost and quality-of-life estimates

Health-related costs and quality-of-life (health state utility) adjustments were assigned to each clinical event and health state in annual cycles. We included all direct medical costs regardless of who paid for them. Cost estimates obtained from earlier years were inflated to 2018 Thai Baht equivalents using the World Bank Gross Domestic Product deflator [65] The cost of HIV management was based on estimates by Over *et al.* [42] and rates of second-line ART use from TAHOD [43]. Drug costs across HIV clinics in Thailand are variable, however, we are not aware of any formal analysis. To best account for this uncertainty, we have used the 2018 unit prices published by Thailand's National Drug System Development Committee [51] and varied these estimates widely in sensitivity analyses. Other costs were based on published estimates for the general population (see Table 2). Most quality-of-life adjustments were based on data from the 2017 Global Burden of Disease study [52]. Since patients using ART are already required to take at least one daily pill, we assumed that remembering to take a daily statin and the inconvenience of doing so (pill burden) was not associated with a quality-of-life decrement. Earlier studies among the general population have similarly assumed regular statin use is not associated with a pill burden [53]. Future costs and benefits were discounted at 3% per year [54].

2.5 | Outcomes

The primary outcome was the incremental cost-effectiveness ratio (ICER; defined as the cost per QALY gained). The threshold for an intervention being deemed cost-effective (willingness-to-pay threshold) was defined as an ICER below 160,000 Baht ($US5315), as recommended by the Health Intervention and Technology Assessment Program, Ministry of Public Health, Thailand [66]. Our secondary outcomes included incremental QALYs gained, incremental costs incurred, incremental life-years gained and the incremental cost per life-year gained.

2.6 | Sensitivity analyses

We used sensitivity analyses to evaluate the robustness of our results to uncertainty in key input parameters. In deterministic sensitivity analyses we varied one or two input parameters at a time while holding others constant at their base-case

estimates. In probabilistic sensitivity analyses we varied multiple input parameters across prespecified distributions over 500 iterations. Beta distributions were used for utilities and event probabilities, and log-normal distributions were used for hazard ratios, safety and efficacy measures, and costs.

2.7 | Scenario analyses

In addition to our sensitivity analyses, we investigated the following scenarios to explore different methodological choices:

1 Restricting the intervention to PLHIV at> 1% risk of CVD in the next five years (as defined by the D:A:D equation). In this scenario and in scenario 2 described below, we assumed an annual cost of 660 Baht ($US21.20)/person for blood lipid testing while an individual's CVD risk score remained below the threshold for starting a statin [15]. We also performed analyses without this assumption to account for the availability of CVD risk equations that do not use blood lipid test results [57].
2 Restricting the intervention to PLHIV at> 5% risk of CVD in the next five years (as defined by the D:A:D equation).
3 Using the Rama-EGAT equation to calculate MI and ischaemic stroke risk in place of the D:A:D equation. The Rama-EGAT equation was developed using data from a study of 3499 HIV-negative Thais [67] and has been validated in the general Thai population [68]. It calculates CVD risk based on age, sex, diabetes status, current smoking status, total cholesterol, HDL cholesterol and systolic blood pressure.[57] Although CVD risk equations based on the general population often underestimate CVD risk in PLHIV [69,70], the Rama-EGAT and D:A:D equations have been shown to produce similar estimates of CVD risk in PLHIV in Thailand [58].

2.8 | Software

Data management and statistical analysis was conducted using SAS 9.4 (SAS Institute Inc, Cary, NC, USA). Modelling was performed in TreeAge Pro 2019 Version R1.0 (TreeAge Software, Williamstown, MA, USA).

3 | RESULTS

3.1 | Base-case analysis

Modelled incidence rates for MI, ischaemic stroke and fatal CVD among the no statin group were 4.7, 2.2 and 2.5 per 1000 person-years respectively. These figures are consistent with observed rates of CVD reported for similarly aged participants in TAHOD [71]. The all-cause mortality rate in the no statin group was 33.9 per 1000 person-years and, over the next 20 years, patients were projected to accumulate a discounted average of 12.211 QALYs, 12.266 life-years and 755,076 Baht ($US24,232) in direct medical costs (Table 3).

Pravastatin was estimated to be less effective and less cost-effective than pitavastatin and was therefore dominated by extension (extended dominance) by pitavastatin (Figure S7). Compared with patients in the no statin group, patients receiving pitavastatin had 21.3%, 22.7% and 16.0% reductions in the incidence of MI, ischaemic stroke and fatal CVD, respectively, and accumulated 0.042 additional QALYs at an incremental cost of 96,442 Baht ($US3095), giving an ICER of 2,300,000 Baht ($US73,812)/QALY gained (Table 3).

3.2 | Sensitivity analyses

Our one-way sensitivity analysis results for pravastatin versus no statin and pitavastatin versus no statin are presented in full in Figures S8,S9 respectively. Base-case findings were sensitive to changes in annual drug cost and drug efficacy. However, even at the lower end of our price ranges for pravastatin (3784 Baht ($US121.40)) and pitavastatin (4091 Baht ($US131.30)) neither was cost-effective compared to no statin. At a willingness-to-pay threshold of 160,000 Baht ($US5,315)/QALY gained, the annual cost of pravastatin needed to drop to 415 Baht ($US13.30; 5.5% of base-case price) to become cost-effective compared to no statin, and the annual cost of pitavastatin needed to drop to 600 Baht ($US19.30; 7.3% of base-case price) to become cost-effective compared to no statin. When the probability of CVD while using a statin was reduced by 30% to account for the possibility of statins exhibiting CVD preventative efficacy in PLHIV beyond that associated with cholesterol improvement, the ICER for pitavastatin versus no statin improved to 1,130,000 Baht ($US36,264)/QALY gained. In a two-way sensitivity analysis, where the probability of CVD while using pitavastatin was reduced by 30%, the annual cost of pitavastatin needed to drop to 1350 Baht ($US43.30; 16.5% of the base-case price) to become cost-effective compared with no statin (Figure 1).

In our base-case analysis, we assumed that the pill burden associated with daily statin use did not cause any quality-of-life decrement. When a decrement was assumed, the average number of QALYs accumulated in the active treatment arms was reduced substantially. At the upper bound of our sensitivity range (0.00384 QALYs lost per year, the equivalent of losing four weeks of perfect health over 20 years [53]), both pravastatin and pitavastatin resulted in a net QALY loss compared to no statin use.

A time horizon longer than that used for the base-case analysis resulted in more favourable ICERs for both the pravastatin versus no statin and pitavastatin versus no statin comparisons. For example when the time horizon was extended to 30 years, the pitavastatin versus no statin ICER improved to 1,530,000 Baht ($US49,101)/QALY gained.

In our probabilistic sensitivity analysis, pravastatin and pitavastatin were not cost-effective in any simulation at a willingness-to-pay threshold of 160,000 Baht ($US5315)/QALY gained (Figure 2).

3.3 | Scenario analyses

The results of our scenario analyses are displayed in Table 3. In all scenarios, pitavastatin remained dominant (extended) over pravastatin. Treating only patients at> 1% risk of CVD in the next five years (Scenario 1) slightly improved the ICER for pitavastatin versus no statin to 2,270,000 Baht ($US72,812)/QALY gained. Restricting statin therapy to only those at> 5% risk of CVD in the next five years (Scenario 2) further improved the ICER for pitavastatin versus no statin to 844,000 Baht ($US27,086)/QALY gained. The ICERs comparing pitavastatin versus no statin in Scenarios 1 and 2

Table 3. Incremental cost-effectiveness of pravastatin and pitavastatin for primary prevention of CVD among PLHIV over 20-year time horizon

Intervention	Total cost, Baht	Statin cost, Baht	Lipid testing cost, Baht	MI[a]	Ischaemic stroke[a]	Fatal CVD[a]	All-cause mortality[a]	Life-years	QALYs	Incremental cost, Baht	Incremental life-years gained	Incremental QALYs gained	Baht/life-year gained[b]	ICER, Baht/QALY gained[b]
Base-case														
No statin	755,076	0	0	4.7	2.2	2.5	33.9	12.266	12.211	–	–	–	–	–
Pravastatin 20 mg	844,370	90,517	0	3.9	1.9	2.2	33.6	12.290	12.241	Dominated (extended)				
Pitavastatin 2 mg	851,518	98,099	0	3.7	1.7	2.1	33.5	12.300	12.253	96,442	0.034	0.042	2,862,000	2,300,000
Scenario 1) Treat those with> 1% risk of CVD in the next five years														
No statin	755,076	0	0	4.7	2.2	2.5	33.9	12.266	12.211	–	–	–	–	–
Pravastatin 20 mg	837,599	83,237	1125	3.9	1.9	2.2	33.6	12.288	12.239	Dominated (extended)				
Pitavastatin 2 mg	844,207	90,210	1125	3.7	1.8	2.1	33.5	12.297	12.251	89,131	0.031	0.039	2,845,000	2,270,000
Scenario 2) Treat those with> 5% risk of CVD in the next five years														
No statin	755,076	0	0	4.7	2.2	2.5	33.9	12.266	12.211	–	–	–	–	–
Pravastatin 20 mg	778,141	22,540	6004	4.2	2.1	2.3	33.7	12.286	12.234	Dominated (extended)				
Pitavastatin 2 mg	779,926	24,484	6004	4.0	2.0	2.2	33.7	12.291	12.241	24,850	0.025	0.029	977,000	844,000
Scenario 3) Using Rama-EGAT equation														
No statin	757,759	0	0	6.0	2.9	2.9	34.3	12.251	12.192	–	–	–	–	–
Pravastatin 20 mg	846,384	89,993	0	5.4	2.5	2.6	34.0	12.272	12.218	Dominated (extended)				
Pitavastatin 2 mg	853,007	97,396	0	5.3	2.4	2.5	33.9	12.276	12.223	95,248	0.024	0.031	3,902,000	3,090,000

Incremental cost-effectiveness for each strategy was measured relative to the next best strategy in terms of QALYs gained. Pravastatin is dominated (extended) by pitavastatin as pravastatin has a higher ICER compared with no statin and is less effective than pitavastatin. Costs, QALYs, and life-years were discounted at 3%/year. Costs can be converted to $US by dividing by 31.16. CVD, cardiovascular disease; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; QALY, quality-adjusted life-year; Rama-EGAT, Ramathibodi-Electricity Generating Authority of Thailand.

[a]Per 1000 person-years; [b]rounded to nearest thousand.

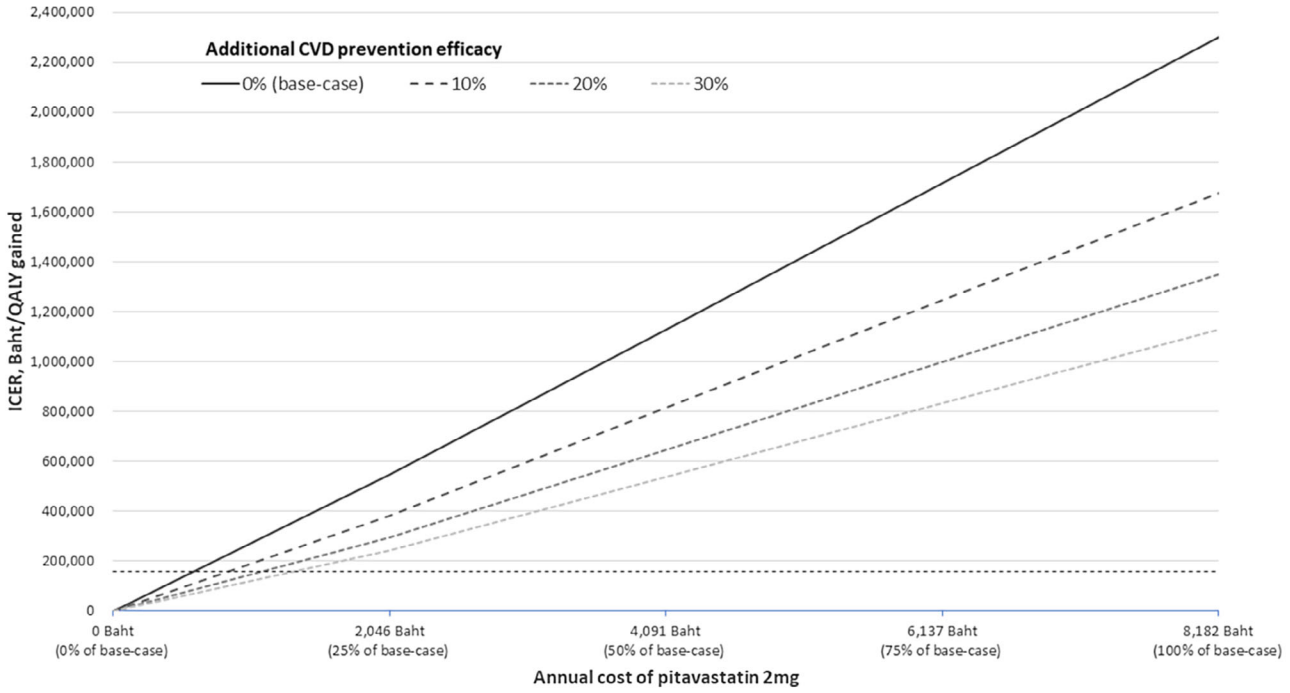

Figure 1. ICER for pitavastatin vs. no statin under various assumptions for pitavastatin cost and additional CVD prevention efficacy.
†The probability of CVD while using pitavastatin was reduced by various percentages to account for the possibility of preventative efficacy beyond cholesterol improvement in PLHIV; Horizontal dashed line represents a willingness-to-pay threshold of 160,000 Baht/QALY gained; Costs can be converted to $US by dividing by 31.16; ICER, incremental cost-effectiveness ratio; CVD, cardiovascular disease; PLHIV, people living with HIV; QALY, quality-adjusted life-year.

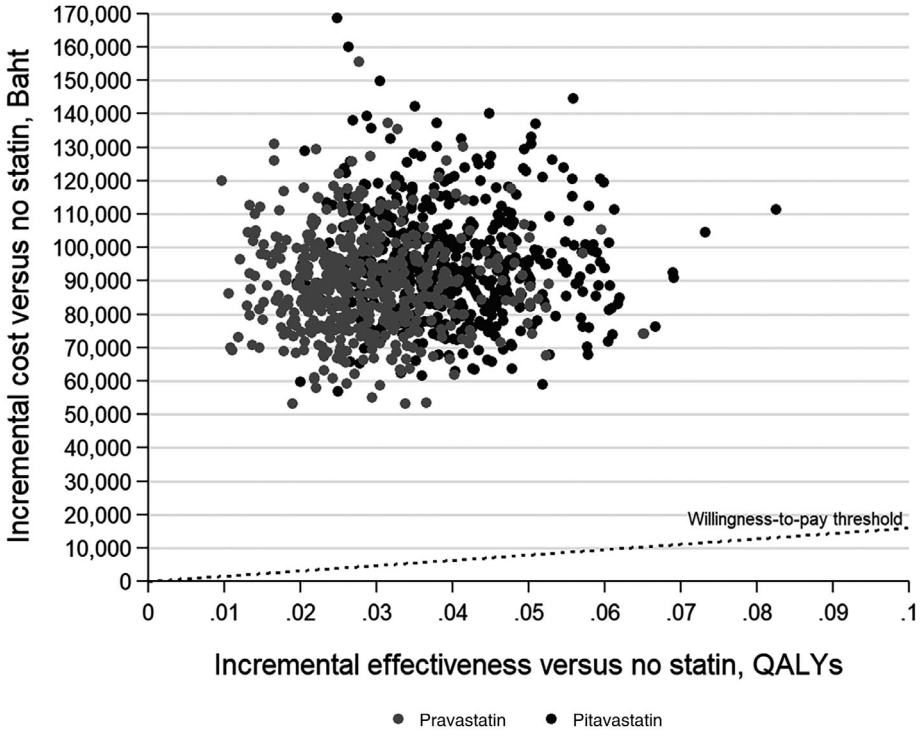

Figure 2. Probability sensitivity analysis scatter plot of incremental cost and incremental effectiveness for pravastatin and pitavastatin versus no statin.
Willingness-to-pay threshold defined as 160,000 Baht/QALY gained; Costs can be converted to $US by dividing by 31.16; QALY, Quality-adjusted life-year.

Box 1. Further research questions

- Do the anti-inflammatory properties of statins reduce the probability of CVD in PLHIV beyond what is achievable with cholesterol improvement?
- Is there a quality-of-life decrement associated with taking an additional daily pill among PLHIV?
- To what extent can the current cost of pravastatin and pitavastatin in Thailand be reduced?
- Could cheaper, non-preferred statins be a clinically acceptable alternative to pravastatin and pitavastatin in PLHIV at relatively low risk of CVD?

Box 2. Policy implications of findings

- At current drug prices, neither pravastatin nor pitavastatin are likely to be cost-effective for the primary prevention of CVD among PLHIV in Thailand not currently using lipid-lowering therapy.

improved marginally when we removed the costs associated with blood lipid testing (2,241,000 and 640,000 Baht ($US71,919 and $US20,539)/QALY gained respectively). When using the Rama-EGAT equation in place of the D:A:D equation for estimating CVD risk (Scenario 3), our model predicted higher rates of MI, ischaemic stroke and fatal CVD compared with the base-case. However, costs increased and the number of QALYs gained decreased compared with the base-case (ICER for pitavastatin versus no statin, 3,090,000 Baht ($US99,166)/QALY gained).

4 | DISCUSSION

While expanding pravastatin or pitavastatin use to PLHIV not currently using lipid-lowering therapy would help reduce the excess risk of CVD among PLHIV in Thailand, we estimated that neither option would be cost-effective at current drug prices. Our results were sensitive to statin costs and statin efficacy, the burden associated with taking an additional daily pill, and the targeting of PLHIV based on CVD risk. However, our primary conclusions were robust across a wide range of sensitivity and scenario analyses.

Tamteerano *et al* estimated that generic simvastatin use for the primary prevention of CVD among all Thai adults with a 10-year CVD risk> 2.5% would be cost-effective at a willingness-to-pay threshold of 300,000 Baht ($US9,628)/QALY gained [17]. Similarly, Ribeiro *et al* found that intermediate potency statins (defined as those expected to produce a 30% to 40% reduction in LDL levels) would be cost-effective for the primary prevention of CVD among those in the general population of Brazil with a 10-year CVD risk greater than 5% [16]. There are several reasons our results differ for the HIV population in Thailand. There is a higher frequency of events competing with CVD in PLHIV compared with the general population. While HIV is an independent risk factor for CVD, the absolute burden of CVD death among PLHIV is lower than in the general population because PLHIV more frequently die from other causes [72,73]. Therefore, preventing CVD among PLHIV results in fewer QALYs gained compared with preventing CVD in the general population. PLHIV also have higher background healthcare costs than the general population, and the abovementioned general population studies were able to assume a lower cost of statin use (for example, 296 Baht ($US9.50)/year for generic simvastatin in Tamteerano *et al.* [17]) than we did because of the low potential for drug interactions among the general population when using cheaper statins. Whether cheaper, non-preferred statins could be a clinically acceptable alternative to pravastatin and pitavastatin in PLHIV at relatively low risk of CVD, or whether the current costs of pravastatin and pitavastatin could be reduced, are issues we are currently investigating (Box 1).

An important consistency between our study and that of earlier statin studies was the impact of including a quality-of-life decrement associated with pill burden [53,74]. In our analysis, QALYs gained for pravastatin and pitavastatin quickly became negative compared with the no statin group when we included a small decrement in quality-of-life associated with remembering to take a daily statin and the inconvenience of doing so. Similarly, when a small pill burden was included in their general population model, Pandya *et al.* [74] found that the optimal CVD risk score threshold for statin indication increased three-fold (from 5% to 15% 10-year risk) at a willingness-to-pay of $US150,000/QALY gained. Current estimates of quality-of-life decrement associated with pill use vary widely [75,76]. However, for PLHIV, who are well versed in the importance of good ART adherence, the burden of taking an additional daily pill is likely to be negligible (Box 1).

The average improvement in cholesterol associated with statin therapy leads to a 15% to 20% reduction in major CVD events [11]. It remains unknown whether the anti-inflammatory properties of statins further reduce the probability of CVD in PLHIV. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) study is currently investigating pitavastatin for the primary prevention of CVD in PLHIV at low- to moderate-risk of CVD [77]. This trial is expected to conclude in 2022 and will shed light on the overall CVD preventative efficacy of statins in PLHIV (Box 1). However, we have shown that even if there was an additional 30% decrease in the probability of CVD with statin use in PLHIV (on top of the reduced probability associated with cholesterol improvement) the cost of pitavastatin would still need to drop substantially before it became cost-effective compared with no statin for the primary prevention of CVD in those not already using lipid-lowering therapy. Importantly, REPRIEVE is also investigating the impact of statin use on various non-CVD outcomes, including AIDS-defining illness, non-AIDS-defining cancer, renal disease, and cirrhosis [77]. Although there is a paucity of literature supporting the benefit of statins in preventing non-CVD events [63], such evidence could alter our main findings. It will also be useful to repeat our analysis in different settings as the protocols and costs associated with HIV and CVD in countries outside of Thailand are likely to differ substantially.

There are several limitations to this study. First, there is evidence suggesting that the D:A:D equation underestimates CVD risk among PLHIV. However, this is based on an analysis of the HIV Outpatient Study [78] which underestimates the prevalence of CVD family history – a key variable in the D:A:D equation. Furthermore, we found that our main findings were unchanged when we used the Rama-EGAT equation to calculate MI and stroke risk. Second, although our model includes coronary intervention, MI, stroke and cardiovascular death as elements of CVD, we did not incorporate peripheral artery disease as it is not an outcome included in the D:A:D equation. Recent evidence suggests HIV infection is associated with a 19% increased risk of peripheral artery disease beyond that explained by traditional atherosclerotic risk factors [79]. Third, we had to estimate various model parameters using data from the general population or from high-income settings due to a lack of HIV-specific or resource-limited setting data. While it is plausible that these parameters differ substantially between the general population and PLHIV, or between high-income and resource-limited settings, our sensitivity analyses suggested that this would have minimal impact on our main findings. Finally, we assumed that half doses of pravastatin and pitavastatin in Thai PLHIV would exhibit the same efficacy as typical doses used for non-Asian PLHIV based on prior studies of other statins [62]. If, in fact, pravastatin 40 mg and pitavastatin 4 mg doses are more appropriate for Thai PLHIV, this would increase our cost estimates for both drugs making them less cost-effective compared with no statin.

5 | CONCLUSIONS

At a willingness-to-pay threshold of 160,000 Baht ($US5,315)/QALY gained, neither pravastatin nor pitavastatin were projected to be cost-effective for the primary prevention of CVD among PLHIV in Thailand not currently using lipid-lowering therapy (Box 2). These findings were sensitive to the targeting of PLHIV based on CVD risk, the burden associated with taking an additional daily pill, statin costs and statin efficacy. However, our primary conclusions were robust across a wide range of sensitivity and scenario analyses.

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COMPETING INTERESTS

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AUTHORS' CONTRIBUTIONS

DCB conceived of and carried out the analysis and drafted the manuscript; ATN, PC, AP, EB, MGL, JGK and SB provided critical input to the design of the analysis; RC, SKh, AA, SKi and JR were essential in the collection of patient data; PC and SKi made significant contributions to the parameterization of the model; SKi oversaw the project from start to finish; All authors helped draft the manuscript and have read and approved the final submission.

ABBREVIATIONS

ART, Antiretroviral therapy; CABG, Coronary artery bypass graft; CVD, Cardiovascular disease; D:A:D, Data collection on Adverse Effects of Anti-HIV Drugs; ICER, Incremental cost-effectiveness ratio; MI, Myocardial infarction; PCI, Percutaneous coronary intervention; PLHIV, People living with HIV; QALY, Quality-adjusted life-year; Rama-EGAT, Ramathibodi-Electricity Generating Authority of Thailand; TAHOD, TREAT Asia HIV Observational Database.

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SUPPORTING INFORMATION

Additional information may be found under the Supporting Information tab for this article.

Table S1. Annual probability of developing diabetes by age and sex

Table S2. Annual probability of smoking cessation by age

Table S3. Annual increase in systolic blood pressure (mmHg) by age and sex[†]

Figure S1. Core model structure.

Figure S2. Probability of all-cause death.

Figure S3. Probability of recurrent MI.

Figure S4. Probability of recurrent ischaemic stroke.

Figure S5. Probability of ischaemic stroke after MI.

Figure S6. Probability of MI after ischaemic stroke.

Figure S7. Cost-effectiveness plane.

Figure S8. Tornado plot showing the impact of changes in model parameters on the incremental cost-effectiveness ratio for pravastatin versus no statin.

Figure S9. Tornado plot showing the impact of changes in model parameters on the incremental cost-effectiveness ratio for pitavastatin versus no statin.

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RESEARCH ARTICLE

Layering and scaling up chronic non-communicable disease care on existing HIV care systems and acute care settings in Kenya: a cost and budget impact analysis

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Abstract

Introduction: Like many countries in sub-Saharan Africa, Kenya is experiencing a rapid rise in the burden of non-communicable diseases (NCDs): NCDs now contribute to over 50% of inpatient admissions and 40% of hospital deaths in the country. The Academic Model Providing Access to Healthcare (AMPATH) Chronic Disease Management (CDM) programme builds on lessons and capacity of HIV care to deliver chronic NCD care layered into both HIV and primary care platforms to over 24,000 patients across 69 health facilities in western Kenya. We conducted a cost and budget impact analysis of scaling up the AMPATH CDM programme in western Kenya using the International Society for Pharmacoeconomics and Outcomes Research guidelines.

Methods: Costs of the CDM programme for the health system were measured retrospectively for 69 AMPATH clinics from 2014 to 2018 using programmatic records and clinic schedules to assign per clinic monthly costs. We quantified the additional costs to provide NCD care above those associated with existing HIV or acute care services, including clinician, staff, training, travel and equipment costs, but do not include drugs or consumables as they would be paid by the patient. We projected the budget impact of increasing CDM coverage to 50% of the eligible population from 2021 to 2025, and compared it with the county budgets from 2019.

Results: The per visit cost of providing CDM care was $10.42 (SD $2.26), with costs at facilities added to HIV clinics $1.00 (95% CI: −$2:11 to $0.11) lower than at primary care facilities. The budget impact of adding 26,765 patients from 2021 to 2025 to the CDM programme was 3,088,928 under constant percent growth, and 3,451,732 under steady-state enrolment. Scaling up under the constant percent growth scenario resulted in 12% cost savings in the budget impact. The county programmatic CDM cost in 2025 was <1% of the county healthcare budgets from 2019.

Conclusions: The budget impact of scaling up AMPATH's CDM programme will be driven by annual growth scenarios, and facility/provider mix. By leveraging task shifting, referral systems and partnering with public and non-profit clinics without NCD services, AMPATH's CDM programme can provide critical NCD care to new, rural populations with minimal financial impact.

Keywords: budget impact; chronic care; costing; modelling; integrated; non-communicable disease; HIV

Additional Supporting Information may be found in the online version of this article.

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1 | INTRODUCTION

In low- and middle-income countries (LMICs), the burden of non-communicable diseases (NCD) is rapidly increasing due to ageing populations, lifestyle and dietary changes, rapid urbanization, and improved control of communicable diseases [1]. Of the 14 million annual premature deaths attributable to NCDs, 90% occur in LMICs where availability and use of appropriate NCD services is insufficient, especially in poorer and rural areas [2,3]. In Kenya 14% of adults have three or more risk factors for cardiovascular disease (CVD) and 25% have hypertension or diabetes as of 2015, with models predicting increasing growth [4,5]. The prevalence of NCDs is also rising among the HIV infected population, increasing mortality and further complicating chronic disease treatment including adherence to antiretroviral (ART) medications [6,7]. To address this emerging epidemic, the Kenyan Ministry of Health (MOH) developed the National Strategy for the

Prevention and Control of Non-Communicable Diseases to implement efficient mobilization and utilization of resources [8]. One of the guiding principles of this strategy is integration of non-communicable disease control into existing primary care and HIV treatment platforms, as NCD care had historically only been available in hospitals. In addition to better coordinating treatment for NCD/HIV comorbidities associated with ageing, this strategy leverages the advancements in health systems infrastructure, training, and workforce task-shifting developed for HIV care platforms to address the systemic deficits in chronic disease care [9].

An HIV/NCD modelling study in Kenya estimated that integrated HIV and NCDs could avert more than 43,000 CVD-related deaths over 15 years but that the cost required to fully scale-up the intervention would require a 12% increase in Kenya's total health budget [10]. Another study in Uganda also demonstrated cost-effectiveness of integrated HIV/NCD care but noted that adding this integration would account for 4% of the national HIV budget [11].

Layering chronic disease care into existing HIV programmes, and further expanding that integration within effective primary care platforms, strengthens the capacity of the public-sector healthcare system to treat NCDs under resource constraints [12]. In western Kenya, the Academic Model Providing Access to Healthcare (AMPATH) chronic NCD care programme has been integrated with existing HIV and primary care programmes and shown to be effective for improving retention in care and hypertension control among HIV positive patients, which addresses an important gap in NCD care delivery for this population [13-16]. The flexibility of this integrated model allows for programme expansion based on local needs and existing health system capacity. Policy changes that aim to finance public programmes and increase enrolment in and reimbursements for the National Health Insurance Fund (NHIF) require a clear understanding of the affordability of NCD treatment programmes. To inform the affordability of scaling up chronic NCD care within AMPATH's existing HIV and primary care programme in western Kenya, we measured the cost of the programme from a health system perspective from 2014 to 2018 and modelled the budget impact of increasing programme coverage from 2021 to 2025 (see Research Agenda).

2 | METHODS

2.1 | Study design

We conducted a retrospective costing and applied the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) framework to perform the Budget Impact Analysis (BIA [17]. We measured the incremental costs to the health system of layering the CDM programme into existing outpatient public and non-profit primary care and HIV care platforms in western Kenya. We constructed a static deterministic model to quantify the budget impact of increasing the CDM programme to achieve the health systems NCD treatment target of drug therapy and counselling coverage of 50% of the eligible population [18], which is one of nine voluntary global targets set by the WHO's Global Monitoring Framework for NCDs and adapted for the Kenyan National Strategy for The Prevention And Control of NCDs.

2.2 | Study setting

In western Kenya, the AMPATH provides comprehensive HIV care for more than 140,000 HIV-infected patients throughout a catchment area of over 3.5 million people. In collaboration with the MOH, AMPATH formed its Chronic Disease Management (CDM) programme with the goal of leveraging existing health delivery platforms to expand treatment capacity.

Costing was conducted for all 69 AMPATH-affiliated health facilities providing chronic NCD care, including 23 HIV care facilities. CDM care is delivered in 37 dispensaries, 16 health centres, 15 primary hospitals, and the Moi Teaching and Referral Hospital (MTRH) (Tables S1 and S2).

The CDM programme draws from the model of task-shifting and community partnerships build upon the capacity and willingness of established healthcare delivery systems [19]. In addition to training nurses who are located at the CDM clinics, clinical officers, pharmacists and physicians are based out of regional hospitals, and travel throughout the county to dispensaries, health centres and primary care hospitals for regular NCD visit days, with frequency driven by patient demand and clinician workloads [20-23]. More complex patients are referred to higher levels of care as needed, and the programmatic staff and AMPATH Medical Records System (AMRS) provides consistent chronic disease tracking. The CDM programme was initially delivered on top of AMPATH's HIV care but has since expanded across other existing MOH or not-for-profit facilities, and now accepts NCD patients regardless of HIV status [9]. Partnering with established health facilities enables the CDM programme to provide comprehensive care without having to create new facilities. This study was conducted in the counties of Bungoma, Busia, Kisumu, Nandi, Trans Nzoia and Uasin Gishu, where AMPATH has established local partnerships and variable CDM program penetration.

2.3 | Ethics approval

This retrospective costing and modelling study used de-identified data from the AMRS, which does not require individual informed consent. The Institutional Research and Ethics Committee at the Moi University School of Medicine and the Institutional Review Board at Brown University approved use of these de-identified data and waived informed consent requirements.

2.4 | Input data and sources

We quantified the additional costs of the CDM programme outside of those incurred by the existing primary and HIV care programmes, including training, clinicians, programme and data management staff, medical records though the AMRS and testing/monitoring equipment. Consumables and medications are paid for by patients and were not included in this analysis.

Monthly programme costs from 2014 to 2018 were collected via key informant interviews with programme officers and clinicians, CDM programme records, and AMPATH employee salary scales and standard operating procedures. Facility costs were assigned using monthly patient visits and

the CDM programme's monthly schedule, which captured variation in visit frequency and clinical staff over time (full cost categorizations and facility attributes are provide in Tables S5, S6,S7,S8,S9,S10). Personnel costs included clinician salary, training costs, and programmatic staff salary. Travel costs are incurred when clinical staff travel to facilities from the referral hospitals in each county or MTRH. They are calculated using round trip distance to the geocoded facility location multiplied by the cost per kilometre provided by the AMPATH Care Standard Operating Procedures for Clinical Travel. Costs of equipment used for diagnosis and monitoring were based on market prices and annualized using key informant reports of equipment lifetime under standard use in the programme [24]. All facilities used electronic blood pressure cuffs to assess blood pressure, and glucometer for blood glucose, and either handheld or bench-top laboratory instruments for A1C measurement. Monthly patient visits by clinic were derived from the AMRS reports.

2.4.1 | *Cost analysis*

All costs were standardized to AMPATH's 2018 payment schedules and standard operating procedures, and all calculations used the average 2018 exchange rate of 101.35 Kenya shillings to one United States dollar [25]. Costs analyses include a description of monthly costs per facility and annual mean cost of facilities and patient visits. We assessed the differences in costs between the CDM facilities added to the HIV platform compared to CDM facilities added to a primary care platform controlling for differences in facility levels, transport costs, and time trends, and a non-linear transformation of number of facility visits to account for economies of scale using the following formula:

$$\begin{aligned}\text{Cost} = &\beta_0 + \beta_1 \text{HIV Clinic} + \beta_2 \text{Facility Patient Visits} \\ &+ \beta_3 \log \text{ Facility Patient Visits} + \beta_4 \text{ Facility Level} \\ &+ \beta_5 \text{ Trasport} + \beta_6 \text{ Time Trend}\end{aligned}$$

2.5 | Budget impact model

In the model we included the following incremental costs: clinic visits, clinical staff salary, programmatic staff salary, training, and travel, as well as incremental equipment costs by clinic. We used normative CDM treatment guidelines to transform the incremental patient visit costs to the annual total patient costs based on management plans reflecting the treatment complexity and attrition among the CDM population (see Tables S5,S6,S7,S8,S9,S10 for more detail) [26].

2.5.1 | *Target population*

The BIA estimates the cost of scaling up CVD care including hypertension and diabetes treatment to reach 50% of the eligible population by 2025 for the six counties where AMPATH is partnered with the public health system (Figure 1). The eligible population for the CVD care target are people over 40 with a 10-year CVD risk profile ≥30% or CVD, which is 7.5% of the population ≥40 [5]. Of the six counties, two had achieved the target, and CDM did not need to be further scaled in those counties. The BIA assumptions are provided in Appendix Table S11.

2.5.2 | *Time horizon*

We modelled growth over a five-year time horizon from 2021 to 2025 to align with the 2025 target achievement date of the WHO's Global Monitoring Framework for NCDs and Kenya's National NCD Strategy.

2.5.3 | *Scenario analysis*

We modelled the scale-up needed to achieve these the targeted number of patients within five years per country in two ways: steady-state enrolment where the same number of patients are added annually, and a constant growth percentage where the number of new patients is derived as a percent of the prior year's total patients.

2.5.4 | *Budget holder*

The budget holder is the county government that allocates health funding and care delivery. However, since most health policy and financing is at the national level we also present results for the total programme. As availability of NCD care is very low for this patient population outside of the CDM programme, we did not include a replacement scenario where patients can receive NCD care elsewhere. Due to the short time frame used in the BIA and the need to budget spending in each year, we do not include discounting.

2.5.5 | *Cost inputs*

The cost is quantified separately for each facility level as the largest per patient cost variation was across facility levels. To account for patient-volume economies of scale and limits of individual clinics, the median monthly patient visits for each facility level was used for the incremental cost-per-patient, and to quantify the number of facilities and therefore the amount of addition equipment needed. Equipment costs are included in the year they would be purchased. The proportion of the total additional patients allocated to each facility level is based on historical trends in proportion of patients in each level. The BIA is reported separately for each county and for the whole programme.

2.6 | Sensitivity analyses

We conducted multivariate and univariate deterministic sensitivity analysis of the costs inputs, median patients per facility, and two alternative distributions of new patients across the facility levels, one prioritizing growth in primary care facilities, and another demonstrating equal growth by facility type. We conducted sensitivity analysis on the travel cost using the interquartile range of the whole programme because counties with fewer programmes may be more closely grouped together and would not accurately reflect programme expansion throughout the entire county.

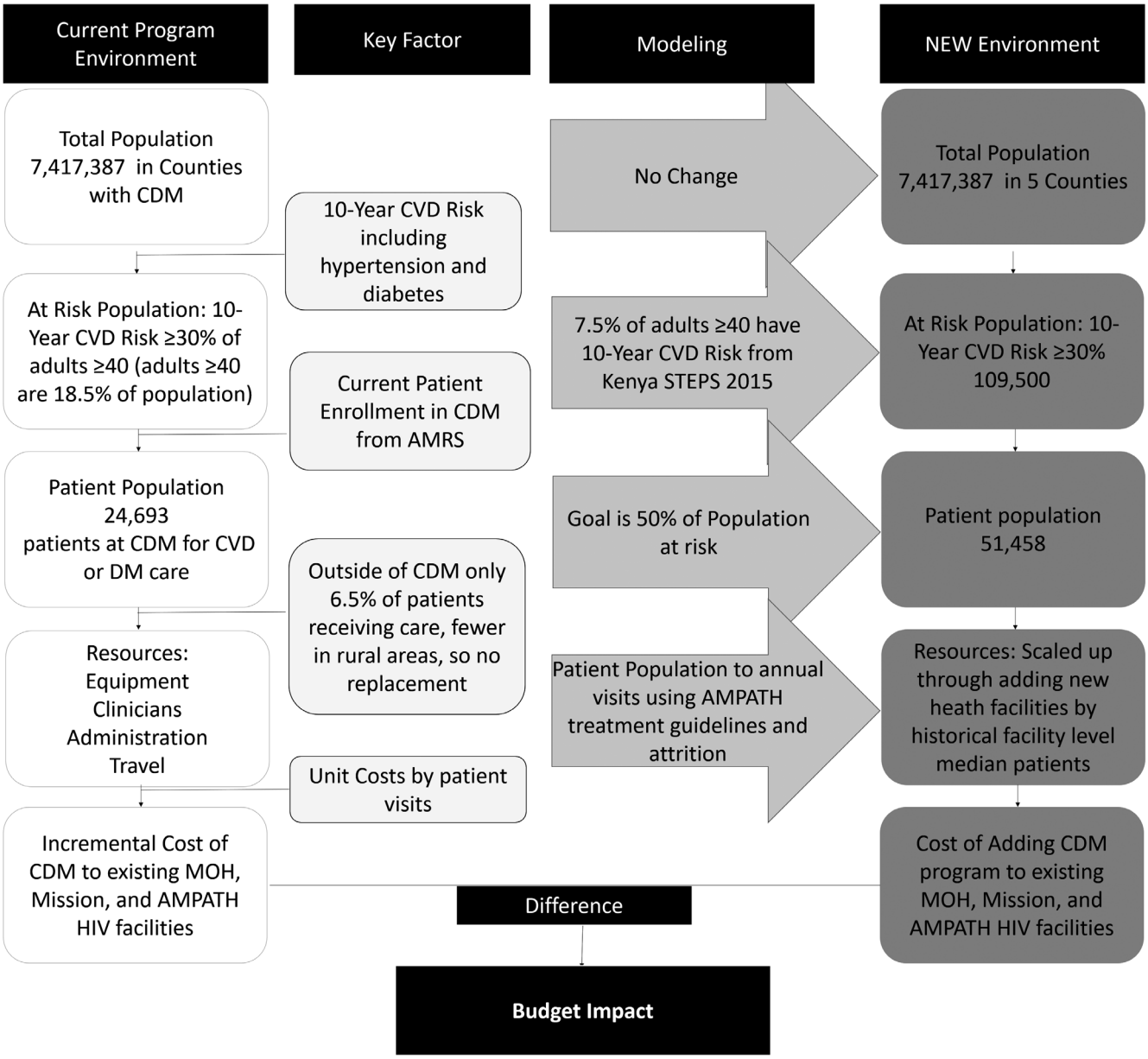

Figure 1. Budget impact schematic. This analysis models the change in total target population, increasing the number of CDM facilities, and predicted increase in NCD prevalence. Adapted from ISPOR Budget Impact-Principals of Good Practice Taskforce [17]. Chronic Disease Management (CDM); cardiovascular disease (CVD); diabetes mellitus (DM); Ministry of Health (MOH); Academic Model Providing Access to Healthcare (AMPATH); AMPATH Medical Records System (AMRS).

3 | RESULTS

Figure 2 provides the monthly costs among active facilities from 2014 to 2018. While the average costs are stable over time, the variation reflects differences in provider visits and monthly patient visits. MTRH is a clear outlier with monthly costs>$3,500 across the study period. There are also distinct distributions in costs by facility type, despite more overlap across the levels of the health system. Because the costing is reflective of a dynamic treatment program that is adaptive to patient demand and programme capacity, the number of facilities and cost of each varies throughout the period of study.

Due to this variation, we separate the levels of care and present the mean and standard deviation (SD) of annual and monthly costs by facility and patient visits in Table 1. The average annual facility cost of CDM varied across the four levels from $3,862 (SD: 373) per dispensary to $72,671 (SD: 10,404) at MTRH. For each level of care, the cost of clinicians and administrative costs made up the largest proportion of total costs. The average total cost per patient-visit ranged from $8.21 (SD: $2.21) at primary hospitals to $18.42 (SD: $3.61) at MTRH. Per facility annualized equipment costs varied by level from $167 (SD 35) to $283 (SD: $39). MTRH had a considerably higher average clinician cost at $64,073

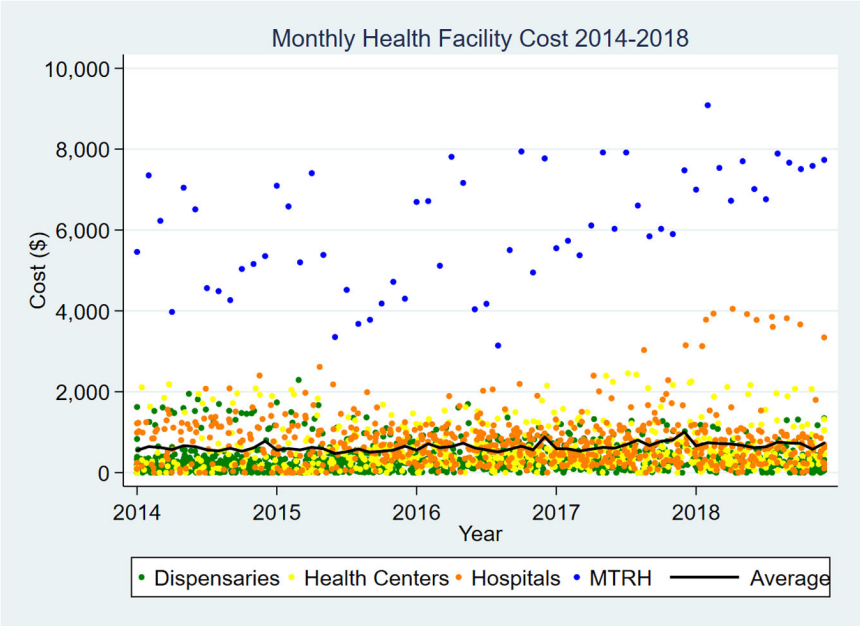

Figure 2. Monthly Programmatic Costs by Facility, and Average Total Cost per Month from January 2014 to 2018. Moi Teaching and Referral Hospital (MTRH)

(SD$10,404). This is unsurprising given that MTRH functions as both a Cardiac Center of Excellence and a referral hospital, seeing both the largest volume of and most complex patients who require a higher proportion of clinical specialists. With the exception of the referral hospital (MTRH), travel costs by visit ranged from $0.80 to $2.99 across all levels of care. Staff costs were evenly distributed by patient visits, with annual costs of $805 per dispensary, $2,002 per health centre, $3,662 per primary hospital and $18,314 at MTRH.

Table 2 presents the difference in patient visit costs for CDM program integration within the HIV care platform compared to the primary care platform. Controlling for patient visits, health care level, transportation costs, and date (month and year), NCD care provision within the HIV care platform was $1 (95% confidence interval (CI), −2.11 to 0.11) less expensive per patient visit compared to care provision added to the primary care platform.

Under the constant percent growth patient enrolment scenario, the incremental five-year budget impact of scaling up CDM across all CDM counties was $3,088,970, while under the steady state scale-up scenario the incremental five-year budget impact was $3,451,732, with a total number of 26,765 new patients enrolled (Table 3). In Bungoma county, the budget impact under the percent growth scale-up and steady-state scenarios is $539,820, and $722,798 respectively, a 34% difference. In Kisumu county, the incremental five-year budget impact under the percent growth scale-up is $287,977 and $390,183 under the steady state scale-up, representing a 35% difference. In Nandi county, the incremental five-year budget impact under the percent growth scale-up and steady state is $2,274,405 and 336,493 respectively, a 23% difference. In Trans Nzoia county, the incremental five-year budget impact under the percent growth scale-up is $187,041 and $202,572 under the steady state scale-up scenario. Savings from the percent growth scale-up scenario in Trans Nzoia is minimal at only 8%. The differences in costs under the two scale-up scenarios are shown for the whole programme in Figure 3, which presents the incremental cost of scale-up by total number of covered patients under all scenarios including sensitivity analysis.

Table 4 presents (1) the 2019 annual healthcare budget for the six counties where AMPATH operates the CDM programme, and (2) the projected total program budget for the most expensive program year for the modelled time horizon (year 2025). The projected per county CDM budget also includes care costs for patients enrolled prior to the scale-up, which allows for a more comprehensive assessment of the proportion of the annual budget that would be needed to provide CDM care to 50% of the eligible population by 2025. The proportion of annual county budget cost is less than 0.9% in every county and scale-up scenario.

3.1 | Sensitivity analysis

Varying the distribution of new patient enrolment across facility types led to limited variation in budget impact (Tables S16, S17,S18,S19,S20,S21). The most expensive distribution was more heavily weighted towards the dispensaries and health centres, while the least expensive option was the one based on historical expansion distribution across facility type. The budget impact using the maximum salaries was between 44% and 48% higher than the budget impact at the lowest level of salaries. The total budget impact of varying the transport costs was minimal (Tables S22,S23).

4 | DISCUSSION

To the best of our knowledge, this is the first study to estimate the health system delivery costs for a public NCD

Table 1. Facility annual cost and cost per patient visit by cost categories in US($) means and standard deviations (SD), 2014 to 2018

	Dispensaries		Health centres		Primary hospital		Referral hospital		Program average	
Cost type	**Facility (SD)**	**Patient visit (SD)**	**Facility (SD)**	**Patient visit (SD)**	**Facility (SD)**	**Patient visit (SD)**	**Facility (SD)**	**Patient visit (SD)**	**Facility (SD)**	**Patient visit (SD)**
Clinicians	1490 (88)	4.43 (0.99)	2356 (361)	3.32 (0.74)	2,947 (163)	2.60 (0.74)	64,073 (19,311)	17.11 (7.17)	301 (40)	5.20 (1.98)
Staff	1548 (278)	4.55 (1.21)	3138 (410)	4.46 (1.21)	5009 (614)	4.49 (1.23)	18,314 (3300)	4.65 (1.17)	270 (21)	4.5 (1.21)
Travel	1068 (449)	2.99 (0.87)	945 (163)	1.32 (0.24)	898 (78)	0.80 (0.19)	0 (0)	0 (0)	79 (20)	1.28 (0.27)
Equipment	167 (35)	0.48 (0.05)	326 (58)	0.46 (0.12)	321 (43)	0.29 (0.08)	283 (39)	0.07 (0.02)	20 (3)	0.33 (0.07)
Total	3862 (373)	11.35 (2.09)	4,268 (404)	9.38 (1.97)	6,9116 (685)	8.21 (2.21)	72,671 (10,404)	18.42 (3.61)	629 (48)	10.42 (2.26)
Volume[a]	19 (5)	29 (38)	10 (3)	63 (69)	11 (3)	101 (134)	1 (0)	341 (114)	42 (8)	63 (14)

[a]Average number of active facilities by month, and average number of patients by facility, with standard deviations.

Table 2. Per patient visit costs by care delivery platform

	Coef.	P> t	[95% Conf. interval]
HIV care platform	−1.00	0.079	(−2.11, 0.12)
Monthly patient visits	0.012	0.002	(0.004, 0.019)
Log (monthly patient visits)	−5.71	<0.001	(−6.22, −5.19)
Facility level			
Health centre	−0.57	0.353	(−1.77, 0.63)
Hospital	0.48	0.455	(−0.77, 1.73)
Referral hospital	20.27	<0.001	(16.68, 23.87)
Date (month/year)	−0.015	0.317	(−0.044, 0.014)
Transportation costs	0.069	<0.001	(0.061, 0.077)
_cons	38.99	<0.001	(19.56, 58.41)

chronic care program in western Kenya integrated into both HIV and primary care platforms, and the first to provide the public health budget impact of scaling up integrated CDM in the region, which results in several policy implications.

While salary for clinicians and programmatic staff were the largest costs, task shifting between clinician levels to increase care coverage while still offering comprehensive care for complex cases reduces costs [9,27-29]. However, human resource constraints may limit proposed scale-up, and needs to be monitored using the CDM needs-based health workforce assessment that can approximate the gaps in human resources as the program grows [26].

The average per patient visit cost was $10.42, and adding CDM to the HIV care platform cost $1.00 less than adding the same CDM services to the primary care platform. However, these findings were not statistically significant so should be considered with caution during program policy. The number of patient visits, facility level and travel demands are different for more remote HIV clinics compared to central hospitals and health centres. Though economies of scale at hospitals would result in a lower overall program budget for these facilities, a key benefit of the CDM programme is its ability to improve access to chronic care in underserved and rural areas. Thus, decision-makers will need to balance efficient care delivery with investments to improve access to care for remote populations.

The budget projections were sensitive to the scale-up model, with average five-year cost savings of 12% if using scaling up with fixed percent growth instead of steady-state enrolment. The model was also sensitive to a lesser extent to the distribution of patient enrolment across facility types, which allows for selection of a lower budget option despite rising patient-visits. While the growth in number of patients over five years is large, the evidence from Busia and Uasin Gishu demonstrates that both rapid programme growth and achievement of the target population coverage are possible. The total annual CDM budget of the fixed percent growth model in 2025, which is the most expensive year of the programme, was very small compared to the total budget. While healthcare financing can be variable, county health budgets have increased by more than 1% every year since 2015. This signifies that the count budgets can support CDM me growth without detracting from existing services [30].

Table 3. Budget Impact of CDM Scale-Up from 2021 to 2025 in US ($)

	Newly enrolled patients	Steady state patient enrolment		Percent growth target		Saving from using percent scale up, %
		Mean	(Min: Max)	Mean	(Min: Max)	
Bungoma	12,834	722,798	(556,910: 861,194)	539,820	(439,830: 642,963)	34
Kisumu	7,578	390,183	(349,735: 510,658)	287,977	(251,687: 367,500)	3
Nandi	5,861	336,493	(271,193: 395,645)	274,405	(222,323: 324,735)	23
Trans Nzoia	3,572	202,573	(165,079: 240,893)	187,041	(152,491: 222,585)	8
Total	26,765	3,451,732	(2,600,555: 4,341,799)	3,088,928	(2,323,970: 3,891,191)	12

[a]Chronic Disease Management (CDM)

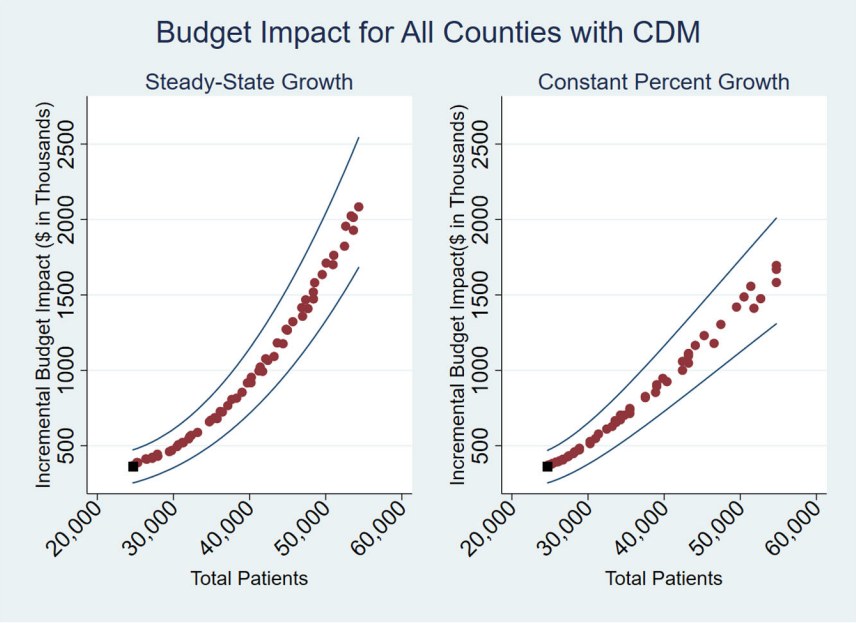

Figure 3. Budget Impact of Scaling up CDM to the treatment targets under two scale-up models: Incremental costs of the additional patients from 2021 to 2025. Chronic Disease Management (CDM)

Table 4. County level annual budget and proportion of budget used by Chronic Disease Management (CDM) in 2025 US($)

	Annual Healthcare Budget (2019)	Steady State Patient Enrolment 2025 CDM Budget	Percent Growth Target 2025 CDM Budget	Proportion of Healthcare Budget, %
Bungoma	30,862,211	263,006	268,323	0.4
Busia	16,908,129	104,881	104,881	0.6
Kisumu	31,039,241	141,750	150,994	0.2
Nandi	19,132,221	122,278	124,568	0.3
Trans Nzoia	21,672,952	110,654	110,715	0.3
Uasin Gishu	20,764,446	163,892	163,892	0.8

Our study has some limitations. We did not explicitly model changes in testing, linkage to care, or changing prevalence of HIV or NCDs. Using set growth rates we are instead able to project easily interpretable estimates of the budget impact, and our approach is consistent with the ISPOR guidelines which prefer static models for shorter timelines [17]. We also did not

Box 1. Research agenda

This research aims to:

- Present findings from a novel budget impact analysis conducted for a dedicated chronic NCD care programme in East Africa.
- Measure clinic-level monthly costs of the AMPATH Chronic Disease Management (CDM) programme in western Kenya, which builds on an establish HIV service platform to provide chronic NCD care to more than 15,000 patients.
- Model the budget impact of increasing the number of annual CDM patients to reach 50% of the eligible population in six counties by 2025.
- Vary the provider costs and type of offering facilities to assess the optimal scenarios under which the CDM program can be scale-up with minimal budget impact.

Box 2. Policy implications and future directions

- Scaling up CDM to the target population coverage under a constant annual growth scenario has a lower five-year budget impact than a steady-stage enrolment.
- The budget impact of scaling up CDM under to the target patient coverage is $3,088,928 ($2,323,970 to $3,891,191).
- The static model used in this BIA is consistent with ISPOR guidelines, which contributes a reliable and adaptable framework for policy makers to estimate the resources required to layer NCD care onto existing health system structures.
- Task-shifting chronic NCD care is a highly cost-saving approach for reaching a wider, rural patient population and one that should be emphasized during scale-up activities.
- The annual total cost of CDM at the target coverage is less than 1% of each county's annual health budget.

account for health system investments to improve pharmacy access or address medication stock outs [31]. In some cases the CDM programme operates concurrently with a Revolving Funds Pharmacy (RFP) model which uses revenue generated from mediation sales to sustainably resupply medications, and is used as a backup in the event of a stock-out at the MoH facility or in the absence of an MoH pharmacy [32]. After the initial startup costs for purchasing medications and hiring pharmacists, the RFP model is largely self-sustaining [21].

AMPATH's CDM programme has lower average per visit costs compared to other public programs that offer chronic NCD care in Kenya, and substantially lower costs than hospitalizations related to untreated NCDs [33,34]. This difference should not disqualify the generalizability of our findings and recommends the expansion of the CDM programme. A challenge in shaping health policy in Kenya is the lack of available evidence indicating that translation of global NCD recommendations is successful in the local context [35]. Certain costs included in this study such as the cost of travel specific to AMPATH clinics, and the differences in provider and staff pay grades compared to the public sector may result in higher total and per patient costs. Therefore, our budget projections can be seen as the higher end of the BIA estimations. The per capita budgets for the counties included in this study are consistent with other counties, which indicates that the low budget impact observed in our projections can be expected to be similar for other countries. AMPATH's CDM programme largely serves rural and peri-urban clinics, and expansion of this program is relevant for the 73% of the national population that reside in Kenya's rural areas. For counties where AMPATH does not have a presence, additional costs for electronic medical records systems will need to be considered in addition to the costs for technicians and data teams included in our analyses [36].

5 | CONCLUSIONS

By relying on task-shifting and diverse facility partnerships, the integrated CDM programme can increase access to chronic NCD care with minimal budget impact in western Kenya. Our budget impact model was highly sensitive to scale-up and human resource costs, and was influenced to a lesser extent by facility mix and travel costs. The programmatic costing and BIA estimates provide policy makers with a framework to estimate resource needs to expand NCD care within existing health system structures, and the flexibility to integrate care within HIV or primary care platforms based on county-level capacity.

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COMPETING INTERESTS

Authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

BO, AM, JL and OG contributed to conception and design. BO and MWB contributed to analysis. All authors contributed to interpretation and important intellectual input. SP, KR, JK and JL contributed to contextual and medical model development and interpretation. BO and OG contributed to first draft of manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

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RESEARCH ARTICLE

Modelling integrated antiretroviral treatment and harm reduction services on HIV and overdose among people who inject drugs in Tijuana, Mexico

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Abstract

Introduction: The HIV epidemic in Tijuana, Mexico is concentrated in key populations, including people who inject drugs (PWID). However, HIV interventions among PWID are minimal, and federal funding was provided for compulsory abstinence programmes associated with HIV and overdose. Alternatively, opioid agonist therapy reduces overdose, reincarceration, HIV, while improving antiretroviral therapy (ART) outcomes. We assessed potential impact and synergies of scaled-up integrated ART and opioid agonist therapy, compared to scale-up of each separately, and potential harms of compulsory abstinence programmes on HIV and fatal overdose among PWID in Tijuana.

Methods: We developed a dynamic model of HIV transmission and overdose among PWID in Tijuana. We simulated scale-up of opioid agonist therapy from zero to 40% coverage among PWID. We evaluated synergistic benefits of an integrated harm reduction and ART scale-up strategy (40% opioid agonist therapy coverage and 10-fold ART recruitment), compared to scale-up of each intervention alone or no scale-up of low coverage ART and no harm reduction). We additionally simulated compulsory abstinence programmes (associated with 14% higher risk of receptive syringe sharing and 76% higher odds of overdose) among PWID.

Results: Without intervention, HIV incidence among PWID could increase from 0.72 per 100 person-years (PY) in 2020 to 0.92 per 100 PY in 2030. Over ten years, opioid agonist therapy scale-up could avert 31% (95% uncertainty interval (UI): 18%, 46%) and 22% (95% UI: 10%, 28%) new HIV infections and fatal overdoses, respectively, with the majority of HIV impact from the direct effect on HIV transmission due to low ART coverage. Integrating opioid agonist therapy and ART scale-up provided synergistic benefits, with opioid agonist therapy effects on ART recruitment/retention averting 9% more new infections compared to ART scale-up alone. The intervention strategy could avert 48% (95% UI: 26%, 68%) of new HIV infections and one-fifth of fatal overdoses over ten years. Conversely, compulsory abstinence programmes could increase HIV and overdoses.

Conclusions: Integrating ART with opioid agonist therapy could provide synergistic benefits and prevent HIV and overdoses among PWID in Tijuana, whereas compulsory abstinence programmes could cause harm. Policymakers should consider the benefits of integrating harm reduction and HIV services for PWID.

Keywords: inject drugs; opioid agonist therapy; HIV; integration; Mexico; overdose; drug treatment

Additional Supporting Information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

As global funding for HIV prevention and treatment programmes declines, service providers will need to maximize the benefits of their programmes by integrating and identifying potential synergies with other health outcomes affecting those populations [1]. This is critical in resource-limited settings like Mexico, which has a concentrated HIV epidemic among key populations including people who inject drugs (PWID), female sex workers and men who have sex with men. In Tijuana, Mexico the withdrawal of Global Fund support resulted in decreased likelihood of PWID obtaining clean syringes [2,3]. Additionally, in 2019, the federal government announced it was suspending funding of civil society organizations responsible for delivering HIV treatment and prevention services [4].

Tijuana, a major city bordering San Diego, California, has one of the highest per-capita rates of injection drug use in Mexico [5]. HIV prevalence among PWID ranges from 4% to 9% [6], and incidence among female PWID is 2.3 per 100 person-years, which is among the highest in North America [7]. PWID in Tijuana additionally experience high rates of mortality (4%/year), with approximately one-quarter of deaths due to drug overdose [8].

Findings from global systematic reviews indicate that opioid agonist therapy, the "gold standard" to treat opioid use disorder [9-11], is effective in reducing HIV transmission [12], improving antiretroviral therapy (ART) outcomes [13], preventing opioid overdoses [14] and reducing recidivism [15]. Despite these benefits, affordable and quality opioid agonist therapy is limited in Tijuana. In 2009, the Mexican government enacted a public-health oriented drug law reform which mandated drug treatment for those apprehended under possession thresholds on their third infraction. However, in 2014, some funding from the federal government to address drug use was allocated to compulsory abstinence programmes. This entailed the forced detention of PWID within abstinence-based drug centres where no evidence-based drug treatment or medical services to address co-morbidities (mental health, infectious or chronic disease) are provided [16,17]. In Mexico, compulsory abstinence programmes have been associated with numerous harms, including increasing odds of non-fatal overdose by 76% (adjusted odds ratio: 95% CI: 1.05 to 2.96) [18] and risk of receptive syringe sharing (RR = 1.14, 95% CI: 1.00 to 1.30) which could facilitate HIV acquisition [16].

A large evidence base supports the synergistic roles opioid agonist therapy can play in improving PWID health. In addition to reducing opioid overdose risk [14], global systematic reviews/meta-analyses found that opioid agonist therapy reduced the risk of HIV acquisition by 54% [12] and PWID living with HIV on opioid agonist therapy were 1.68 times more likely to be recruited into HIV care and 23% less likely to drop off of ART [13]. Opioid agonist therapy can reduce reincarceration [15], further reducing HIV [19] and fatal overdose, which is significantly elevated within the first few weeks after release [20].

Mathematical modelling can aid policymakers in making evidence-based decisions on scaling-up interventions to enhance public health impact [1,21]. Our previous modelling of Mexican drug policy reforms found limited HIV impact due to improper implementation. However, if the reform were correctly implemented, then it could have averted over 20% of new HIV infections among PWID in Tijuana by 2030 [16]. Given changing drug policies and HIV funding landscape, our aim was to assess the potential synergies and benefits of an integrated HIV and harm reduction response on HIV and overdose among PWID in Tijuana.

2 | METHODS

2.1 | Model structure

We extended our previously published dynamic, deterministic model of HIV transmission (sexual- and injecting-related) among PWID in Tijuana [16] to explicitly include fatal overdose and additional opioid agonist therapy effects/synergies on overdose, ART and reincarceration – (Figure S1). Briefly, the model was stratified by sex (male or female), incarceration history (never, in prison, recently incarcerated (past six months), not recently incarcerated), recent police harassment (having syringe confiscated by police or not), opioid agonist therapy or compulsory abstinence programme status (on/off) and HIV stage (susceptible, acute, latent, pre-AIDS, AIDS) and ART status (see Supplementary material). We modelled injection and sexual transmission as a function of the number of syringe sharing acts, unprotected sex acts, proportion of sexual partners who injected drugs, probability of transmission from risky injection- or sexual-related exposures, HIV prevalence and weighted HIV stage among partners (with greater transmissibility due to higher viraemia if in the acute or pre-AIDS stage compared to the latent stage) [22,23]. We assumed ART reduced HIV mortality, sexual HIV transmission and injecting-related HIV transmission [24]. We assumed proportionate mixing with regards to syringe sharing. Sexual transmission was exclusively heterosexual between PWID and their sexual partners who injected and did not inject drugs.

Figure 1 provides a conceptual overview of how opioid agonist therapy and compulsory abstinence programmes interact with HIV prevention, ART and overdose outcomes in the model. We explicitly incorporated fatal overdose, with elevated risk of overdose within the first four weeks after release from prison [14]. Fatal overdose was reduced by 79% when on opioid agonist therapy, with small elevated risks of fatal overdose upon entering and exiting opioid agonist therapy [14]. We assumed risk of HIV acquisition was reduced while on opioid agonist therapy [12]. Based on a meta-analysis, recruitment and retention on ART were elevated among people on opioid agonist therapy compared to those not [13]. We also included reduced risk of reincarceration among PWID on opioid agonist therapy [20]. Additionally, ever being exposed to compulsory abstinence programmes increased receptive syringe sharing by 14% [16]. It is unclear whether this elevated risk in syringe sharing occurs during and/or after exposure, or whether this association is causal. Findings from incarcerated settings, where drug use is prohibited, indicate that fewer PWID continue to inject drugs while confined. However, risky injection practices such as syringe sharing occur more frequently due

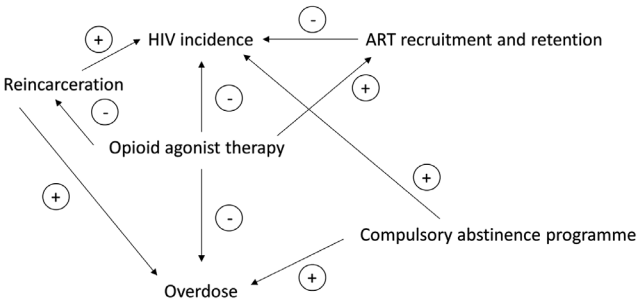

Figure 1. Conceptual model of association between opioid agonist therapy and compulsory abstinence programmes on HIV- and drug-related outcomes.
Plus and minus signs correspond to direction of association between exposure (opioid agonist therapy or compulsory abstinence programme) and the outcome (e.g. opioid agonist therapy reduces the risk of overdose (-) while compulsory abstinence programmes increased the risk (+)).

to limited availability of clean syringes [25,26]. Thus, we implemented the effect of compulsory abstinence programmes exposure in the model by assuming a 14% increase (varying from 0% to 30%) in receptive syringe sharing among PWID while in these programmes. Evidence from Tijuana also indicated that compulsory abstinence programmes were associated with 76% higher odds of recent overdose compared to PWID with no recent exposure [18]. Due to limited data, we assumed that risk of fatal overdose associated with compulsory abstinence programmes would be equivalent to non-fatal overdose risk.

2.2 | Model parameterization and calibration

The model was primarily parameterized by demographic and behavioural data from El Cuete IV, a longitudinal cohort of PWID in Tijuana followed from 2011 to 2020 [27]. The El Cuete IV study protocol was approved by the UCSD Human Subjects Protections Program and El Colegio de la Frontera Norte in Tijuana and all participants consented to study procedures. We calibrated to HIV prevalence by sex and incarceration history (in 2005, 2006 and 2011), HIV incidence (in 2014), and ART coverage among HIV-infected PWID (in 2012). See supplemental material and Borquez *et al* [16] for calibration details. We assumed ART scale-up began in 2003, varying uniformly to reach 2% to 18% coverage in 2012 [28,29]) (Figure S2), and no opioid agonist therapy based on low current methadone use (<5% in 2016 to 2018). We sampled 120,000 parameter sets from assigned prior distributions using Latin Hypercube Sampling, calculating the total log-likelihood as the sum log likelihoods for each of our calibration parameters, and selecting runs producing total log-likelihoods above the 99th percentile for the final analysis; 201 runs were selected with most projections within the 95% uncertainty intervals (UI) of the data (Figures S3, S4). Key parameters related to ART, opioid agonist therapy, compulsory abstinence programmes and overdose are in Table 1. The remaining model parameters and calibration values are in Tables S1, S2 respectively. Overdose deaths in Mexico are not officially monitored or reported. The overdose rate was therefore based on an epidemiological study using El Cuete IV data which used both confirmed and unconfirmed cause of death information [8]. Given uncertainty and challenges in confirming deaths and inconsistencies in reporting "overdose" or "drug toxicity" as cause of death, we instead used it to generate the overdose mortality rate rather than for calibration.

2.3 | Modelled scenarios and outcomes

We assessed the relative benefits of an integrated harm reduction and HIV response, compared to scale-up strategies which focused on only one aspect, and potential synergistic effects of this integration through ART. As such, we first examined the impact of each component of opioid agonist therapy scale-up (through its effects on ART recruitment/retention, HIV transmission, and/or incarceration) on HIV incidence, fatal overdose and ART coverage. We then assessed the total and synergistic benefits of combined integrated opioid agonist therapy and ART scale-up, compared to impact of scale-up of each intervention alone (opioid agonist therapy or ART) or no scale-up. Finally, given funding of compulsory abstinence programmes, we explored potential harms of scale-up of this intervention only.

1. Status quo. No opioid agonist therapy and low ART coverage (ranging from 2% to 18% virally suppressed on ART in 2012).
2. Opioid agonist therapy scale-up to 40% coverage among PWID from 2020. 40% coverage considered by the World Health Organization to be the threshold for high coverage [34] (Figure S5).
   a. Simulating opioid agonist therapy effect on improving ART recruitment/retention only.
   b. Simulating opioid agonist therapy direct effect on reducing HIV acquisition only.
   c. Simulating full effects: reduced HIV acquisition, increased ART recruitment/retention, reduced reincarceration.
3. ART scale-up. Recruitment of ART was increased ten-fold from 2020, reaching a mean of 56% of HIV-infected PWID on ART by 2030 (similar to current national ART coverage estimates in Mexico [35]).
4. Integrated ART and opioid agonist therapy scale-up. ART recruitment increased ten-fold, opioid agonist therapy scaled-up to 40% among PWID from 2020. We adopted a broad definition of "integrated opioid agonist therapy and HIV services" as it has been implemented either through coordination of services [36] or collocation in one clinical setting [37,38].
   a. Simulating opioid agonist therapy effect on ART recruitment/retention only
   b. Simulating full opioid agonist therapy effects: reduced HIV acquisition, increased ART recruitment/retention, reduced reincarceration.
5. Compulsory abstinence programme scale-up to 40%. Compulsory abstinence programme scaled-up from zero to 40% coverage among PWID from 2020.

We projected HIV prevalence, HIV incidence, ART coverage and fatal overdose among PWID until 2030. We estimated the proportion of new HIV infections and fatal overdoses averted from 2020 to 2030 between each scenario and the status quo (base case). To assess synergies between opioid agonist therapy and ART, we calculated the difference in the cumulative number of HIV cases from 2020 to 2030 in the integrated scale-up scenario and the ART scale-up only scenario.

2.4 | Sensitivity analyses

We explored impact of uncertainty in intervention parameters on projections of HIV and overdose impact with the integrated OAT and ART scenario compared to the status quo. We conducted several one-way sensitivity analyses by varying: opioid agonist therapy duration (six months or two years, compared to one year at baseline), opioid agonist therapy effect estimate ("best case scenario" using upper bound values for all effects on ART recruitment retention, HIV transmission, reincarceration and overdose, and a "worst-case scenario" using the lower bound effect estimates). Due to uncertainty in compulsory abstinence programme effects, we explored how

Table 1. Key model input parameters associated with opioid agonist therapy, compulsory abstinence programmes and HIV treatment, prevention and overdose outcomes

Parameter	Symbol	Sampled point estimate and 95% confidence interval	Sampling distribution	Reference/notes
Fatal overdose rate (per year)	μ	0.01 (0.008 to 0.012)	Uniform	[8]
Relative risk of overdose if on opioid agonist therapy (OAT) compared to off opioid agonist therapy	$RROD^{OAT}$	0.21 (0.13 to 0.34)	Lognormal	[14]
Relative risk of overdose if in compulsory abstinence programme compared (CAP) to no compulsory abstinence programme	$RROD^{CAP}$	1.76 (1.05 to 2.96)	Lognormal	[18] Assumed similar to risk of non-fatal overdose for recent compulsory abstinence programme exposure
Relative risk of fatal overdose within first four weeks after entering opioid agonist therapy compared to being enrolled in opioid agonist therapy programme	$RROD^{OATin}$	1.97 (0.94 to 4.10)	Lognormal	[14]
Relative risk of fatal overdose within first four weeks after exiting opioid agonist therapy compared to being enrolled in opioid agonist therapy programme	$RROD^{OATout}$	2.38 (1.51 to 3.74)	Lognormal	[14]
Relative risk of being recruited on to ART if on opioid agonist therapy compared to off opioid agonist therapy	$RR^{ARTrecruit}$	1.69 (1.32 to 2.15)	Lognormal	[13]
Relative risk of ART discontinuation if on opioid agonist therapy compared to off opioid agonist therapy	$RR^{ARTdropout}$	0.77 (0.63 to 0.95)	Lognormal	[13]
ART discontinuation rate per year	ψ	0.06 (0.02 to 0.10)	Uniform	[30]
Rate of opioid agonist therapy or compulsory abstinence programme cessation (/year)	δ	1 year (varied from 6 months to 2 years in sensitivity analyses		Duration on opioid agonist therapy or compulsory abstinence programmes was assumed to be one year, consistent with the average duration of opioid agonist therapy in low/middle income settings [31]. Average duration in compulsory abstinence programmes in Mexico remains unknown [32] but presumed to average between six months and one year.
Relative risk of recidivism if on opioid agonist therapy compared to off opioid agonist therapy	RR^{recid}	0.80 (0.71 to 0.90)	Lognormal	[15]
Relative risk of fatal overdose within first four weeks of release from prison compared to being in opioid agonist therapy programme	$RROD^{prison}$	1.7 (1.3 to 2.2)	Lognormal	[20]
Relative efficacy of ART on parenteral transmission	RR^{ARTinj}	0.5 (0.25 to 0.75)	Uniform	[24] Uncertain, varied widely
Relative efficacy of ART on sexual transmission	RR^{ARTsex}	0.07 (0.02 to 0.22)	Lognormal	[33]
Relative risk of HIV transmission if on opioid agonist therapy compared to not on opioid agonist therapy	RR^{HIVOAT}	0.46 (0.32 to 0.67)	Lognormal	[12]

Table 1. (*Continued*)

Parameter	Symbol	Sampled point estimate and 95% confidence interval	Sampling distribution	Reference/notes
Relative risk of receptive syringe sharing if in compulsory abstinence programme (CAP) compared to not in compulsory abstinence programme	RR^{CAP}	1.14 (1.00 to 1.30)	Lognormal	[16] Assumed similar to risk observed among those ever exposed to compulsory abstinence programme versus not

Other model parameters and calibration data can be found in Tables S1, S2.

impact of compulsory abstinence programme scale-up varied with a "best-case scenario" using the lower bound impact on elevated syringe sharing and overdose, and "worst-case scenario" using upper bound impact.

3 | RESULTS

In the status quo scenario, our model projected HIV prevalence to increase from 3.6% in 2020 to 4.8% in 2030. Figure 2 and Figure S6 show the impact of various intervention scenarios and components on new HIV infections (Figure 2A, Figure S6A) and fatal overdoses (Figure 2B, Figure S6B) among PWID over the next decade. When incorporating the full HIV prevention benefits of opioid agonist therapy (reducing HIV acquisition, increase in ART recruitment/retention, reduced reincarceration), opioid agonist therapy scale-up among PWID could avert 31% (95% UI: 18%, 46%) of new HIV infections over the next decade (Figure 2A), and increase ART coverage from 11% to 21% among HIV-positive PWID (Figure 3). Due to low baseline ART coverage, compared to the status quo, the independent effect of opioid agonist therapy on ART recruitment/retention only prevented 2% of new HIV infections over the next decade, with most of the opioid agonist therapy effect due to reduced HIV acquisition.

Increasing ART recruitment rates by 10-fold elevated ART coverage from 11% in 2020 to 56% in 2030 among HIV-positive PWID, and averted 20% (95% UI: 4%, 42%) of new HIV infections compared to the status quo over the next decade. With integrated opioid agonist therapy and ART scale-up, ART coverage could reach 73% in 2030 and prevent 48% (95% UI: 26%, 68%) of new HIV infections in ten years if all opioid agonist therapy benefits were included compared to the status quo scenario. Importantly, synergistic effects were observed. When incorporating only the opioid agonist therapy effects on ART recruitment and retention, scaling-up integrated opioid agonist therapy and ART (achieving 70% ART coverage among HIV-positive PWID) averted 9% more (95% UI: 2% to 15%) HIV cases (Figure 4) compared to ART scale-up alone (achieving 56% coverage). Conversely, scaling-up compulsory abstinence programmes to 40% coverage (as opposed to opioid agonist therapy) could cause more HIV infections (−8% (95% UI: −22%, 0%)), due to increased risk of syringe sharing among individuals who had experience with compulsory abstinence programmes (Figure 2A) compared to the status quo.

The differential impact of opioid agonist therapy versus compulsory abstinence programme on fatal overdoses is shown in Figure 2B. With 40% opioid agonist therapy coverage among PWID, 22% (95% UI: 10%, 28%) of fatal overdoses could be averted over the next decade. Nearly 20% of this effect could be due to the indirect effect of opioid agonist therapy on reducing reincarceration. Conversely, compared to the status quo, scale-up of compulsory abstinence programmes could result in more overdoses (−26%, 95% UI: −65%, −4%).

3.1 | Sensitivity analyses

Overall impact of integrating OAT with ART on HIV and overdose outcomes was robust. Projections of HIV and overdoses averted deviated <15% with variations in OAT duration and effect estimates compared to the status quo scenario assumptions (Figure S7). Greater impact was achieved through longer duration OAT, or 'best case' scenario effect estimates. The projected impact of compulsory abstinence programme scale-up was less sensitive to uncertainty in HIV effect estimates (<10% relative difference using best or worst case effect estimates), but moderately sensitive to uncertainty in overdose effect (16% fewer overdoses caused using "best-case" effect estimates, 27% more overdoses caused using "worst-case" effect estimates, compared to the baseline scenario.

4 | DISCUSSION

As HIV and overdose are two critical health risks facing PWID, we modelled the potential synergies of an integrated HIV and harm reduction response on HIV incidence and overdose among PWID in Tijuana, Mexico. Over the next decade, integrated scale-up of ART (ten-fold recruitment) and opioid agonist therapy (to 40% among PWID) could avert half of new HIV cases and one-fifth of fatal overdoses among PWID. With concomitant scale-up of ART recruitment, integration of opioid agonist therapy could interact synergistically by improving ART recruitment and retention, resulting in enhanced ART coverage and averting more HIV infections than if opioid agonist therapy were scaled up alone. Conversely, adopting

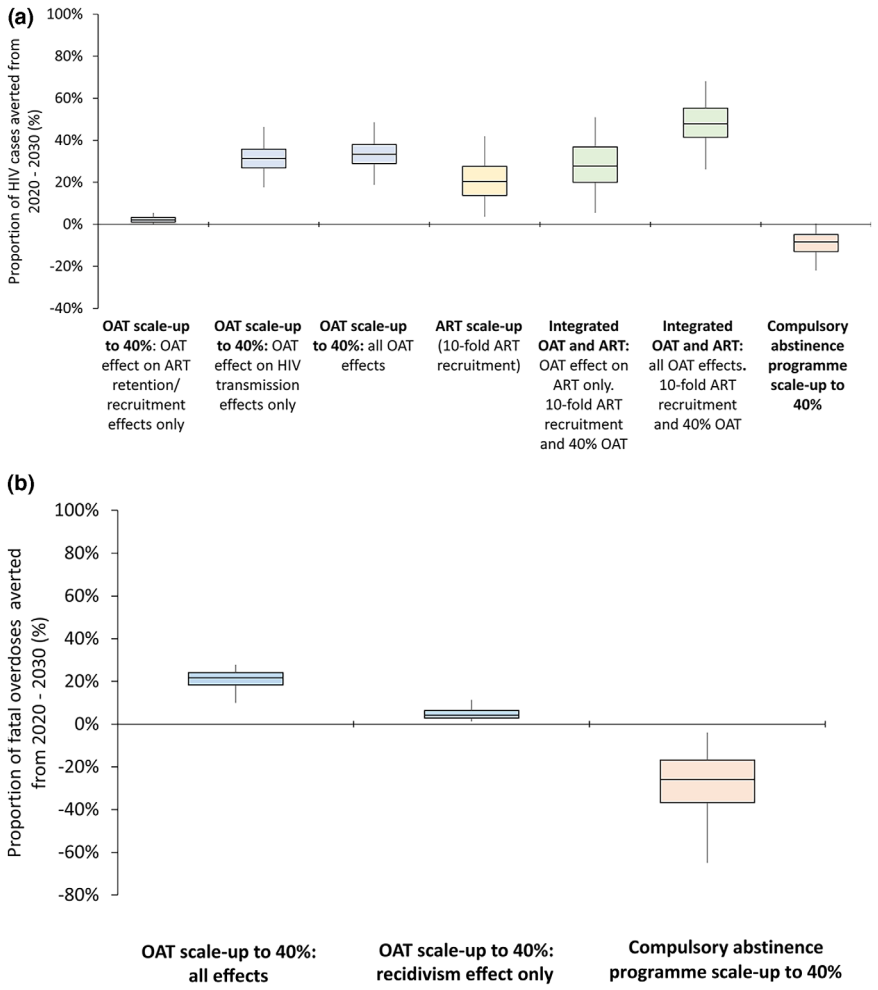

Figure 2. Proportion of HIV cases (A) and fatal overdoses **(B)** from 2020 to 2030 among PWID in Tijuana compared to the base case scenario. Blue boxplots represent opioid agonist therapy (OAT) scale-up to 40% coverage only; yellow boxplot represents 10-fold increase in ART recruitment only; green boxplots represent opioid agonist therapy scale-up to 40% coverage plus increase in ART recruitment by 10-fold. Red boxplots represent scale-up of compulsory abstinence programmes to 40% coverage (instead of opioid agonist therapy).

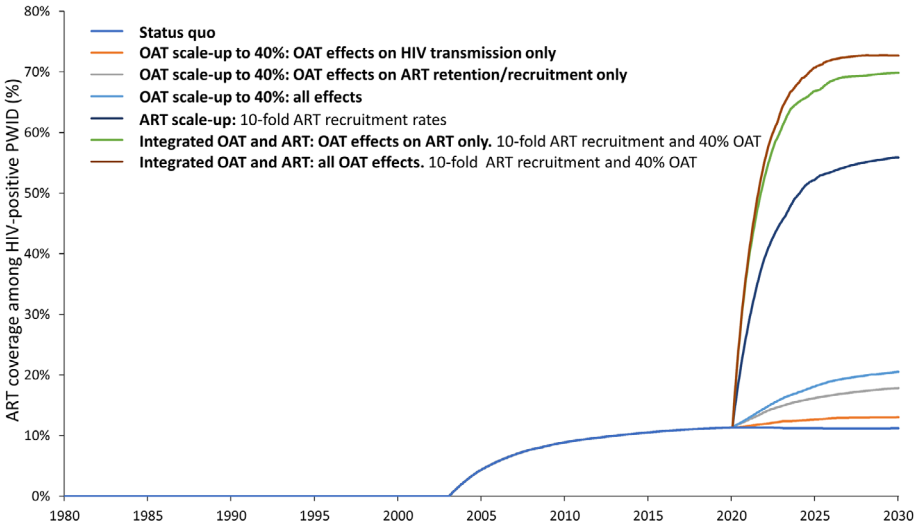

Figure 3. Trajectories of ART coverage levels under various opioid agonist therapy (OAT) and ART scale-up scenarios.

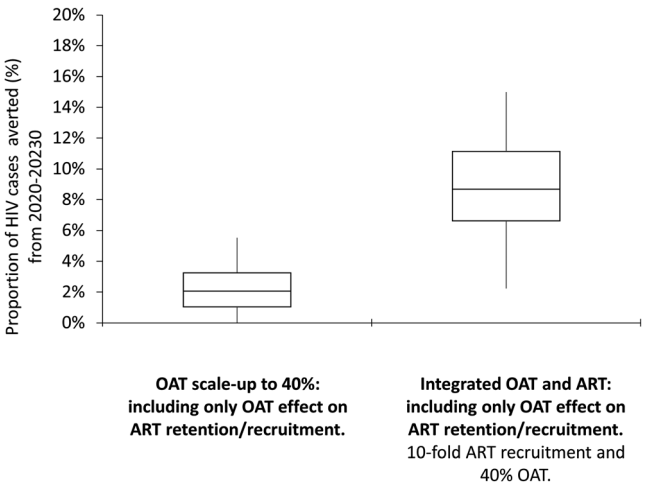

Figure 4. Proportion of HIV cases averted of opioid agonist therapy (OAT) effect on recruitment and retention to ART with and without ART scale-up.
In the scenario with opioid agonist therapy scale-up only, the proportion of HIV cases averted was compared to the base case. In the scenario with opioid agonist therapy and ART scale-up, the proportion of cases averted was compared to ART scale-up only.

non-evidence based approaches to treat opioid use disorder, such as police operations that force PWID to compulsory abstinence programmes, could negatively impact HIV and overdose outcomes [39]. Within the context of drug policy reform, this finding underscores the importance for policymakers to ensure that HIV prevention and care is integrated with evidence-based drug treatment programmes such as opioid agonist therapy to maximize impact and realize synergies (see Box 1).

Despite the potential benefits of an integrated strategy, numerous challenges exist to implementation in Tijuana. First, opioid agonist therapy is prohibitively expensive for PWID. While one 80 mg methadone dose can cost between 3 and 6 USD [40], daily adherence would be difficult as most PWID in Tijuana earn less than $7 per day [6]. Second, police have harassed and arrested PWID outside of treatment centres [41], discouraging their willingness to seek care. For this reason, we partnered with the Tijuana police department to train officers on the benefits of harm reduction and align policing with public health [42]. However, with few available treatment slots and economic barriers to entry [43], it is unlikely police-initiated referral to evidence-based drug treatment will translate to successful enrolment and adherence. Third, although ART is free under the Mexican health care system, barriers to uptake and adherence remain. The main HIV clinic is approximately 25 km from the epicentre of HIV in Tijuana, and PWID experience stigma and discrimination which limit access [44]. To address these barriers, a binational student-run free clinic was established in 2012 in a dense HIV and PWID area to enhance access to HIV testing, treatment and prevention services for key populations [45]. Additionally, local NGOs have provided care to PWID that did not satisfy the requirements to be treated at public services, but logistical difficulties arose around the collection and processing of laboratory samples for monitoring. Full integration of ART and opioid agonist therapy services will require changes to how ART is currently accessed. Greater coordination between opioid agonist therapy and HIV treatment providers will be needed to reach the 90-90-90 targets, which the Mexican government has committed to achieving [35]. By increasing ART recruitment 10-fold and reaching 40% opioid agonist therapy coverage, ART coverage among PWID could reach these targets. However, this is likely optimistic given recent funding cuts to civil society organizations and centralization of ART procurement which has resulted in shortages [4].

Finally, while compulsory abstinence programmes in Tijuana are heterogeneous in terms of quality of care and abuse they inflict [46,47], some of these centres imperfectly fill numerous unmet needs among PWID and their families, including housing and support in times of crisis [47,48]. Integration of services among this marginalized population will need to address these key structural issues. Models in which opioid agonist therapy is provided in outpatient settings alongside centres offering shelter and support (including through religious, mutual and 12 steps models) should be considered. Data on patient outcomes, especially among those living with HIV and on ART, should also be rigorously collected and monitored. Furthermore, economic evaluations are warranted to determine the value-for-money (or lack thereof) of these programmes.

A strength of our study was the incorporation of numerous interacting benefits of opioid agonist therapy on HIV, overdose, ART and incarceration. Our modelling was consistent with previous studies indicating that scale-up of harm reduction such as opioid agonist therapy can have substantial benefits on preventing HIV [16,49,50], and fatal overdoses among PWID [49]. It was also consistent with findings that opioid agonist therapy can improve the HIV prevention benefits of ART [51]. While we did not model the impact of opioid agonist therapy in incarcerated settings, previous modelling has shown substantial benefits of scaling up these services in prisons [52].

As with all modelling, there is uncertainty in several parameter estimates. First, we note that many opioid agonist therapy effect estimates were based on findings from global

Box 1. Policy Implications of integrating HIV and harm reduction response on HIV and overdose among PWID in Tijuana

- **Ensure provision of high-quality, accessible, affordable opioid agonist treatment.** Increasing opioid agonist therapy coverage must be accompanied by other measures that include improving accessibility of opioid agonist therapy through increasing the number and geographical coverage of opioid agonist therapy providers; lowering opioid agonist therapy costs; disseminating information about the benefits of opioid agonist therapy to policymakers, health professionals and law enforcement; establishing a referral system within healthcare settings for people with opioid use disorder and guaranteeing protection of human rights. Greater knowledge of the benefits of these programmes at the community level could reduce stigma and reduce police harassment outside opioid agonist therapy clinics.
- **Ensure high coverage of HIV antiretroviral therapy.** Only a small proportion of PWID are receiving ART in Tijuana, in part because individuals are unaware of their infection and the ART treatment centre is not centrally located. Improvements along the HIV treatment cascade for PWID could be substantially enhanced if opioid agonist therapy and ART services were integrated and provided in a location near to where PWID live or gather.
- **Concomitant scale-up of opioid agonist therapy and ART provision can provide synergistic benefits on HIV and overdose.** Our modelling highlights how opioid agonist therapy and ART can act synergistically by opioid agonist therapy further improving ART recruitment and retention, resulting in enhanced ART coverage compared to if only ART is scaled-up in isolation. Opioid agonist therapy also prevents reincarceration, which can further prevent HIV and overdose. These benefits are in addition to direct benefits of opioid agonist therapy on prevention of overdose, HIV and hepatitis C virus (HCV).
- **Direct funding or referral to evidence-based drug treatment programmes over non-evidenced-based compulsory abstinence programmes.** The government should reconsider any funding and referral to non-evidenced based compulsory abstinence programmes as modelling indicates these programmes might cause more HIV infections and drug-related deaths due to the increased risk of syringe sharing and overdose among individuals who are released from these sites.
- **Scale-up complementary harm reduction services.** While not directly included in our modelling analyses, other harm reduction services will complement opioid agonist therapy and ART provision. The withdrawal of funding from the Global Fund has severely restricted needle and syringe programme provision, and scale-up in access, provision and geographical coverage through formal services and in the community through NGO services and outreach programmes is required to prevent HIV and HCV. Naloxone is not currently available; free distribution and training on administration to health providers, police, first contact persons and PWID are critical to preventing opioid overdose deaths. Establishment of safe injection rooms could also have dual benefits on reducing overdose and preventing HIV.
- **Epidemic modelling can aid policymakers in understanding synergies and multiple benefits of integrated HIV care to inform decision making and resource allocation.** Models can synthesize data on intervention effects and synergies for multiple health outcomes to ensure the full public health impact of integrated care for PWID are understood, to inform evidence-based decision making and resource allocation.

systematic reviews/meta-analyses of studies primarily from high-income settings which might not be generalizable to settings like Tijuana. We have documented structural barriers to opioid agonist therapy in Tijuana, yet once accessed, services are high quality and provide comprehensive support, such as legal services and psychosocial counselling [40]. Second, data from Tijuana indicate an association between recent compulsory abstinence programme attendance and non-fatal overdose, which we assumed was similar for fatal overdose due to lack of data. Additionally, historic exposure to compulsory abstinence programmes is associated with receptive syringe sharing. Both these associations require further studies to confirm causal pathways. Third, we used setting-specific estimates for fatal overdoses, but this rate is highly uncertain due to lacking cause of death information and underreporting of overdoses [8]. However, our results in terms of proportions of overdoses averted should be robust to uncertainty in the absolute overdose rate. Fourth, we neglected polysubstance use, but 15% of PWID in Tijuana report injecting both opioids and stimulants, which could alter the effect of opioid agonist therapy [53]. We purposely limited opioid agonist therapy scale-up to 40% coverage among PWID to account for a proportion who may be ineligible. Fifth, our model was calibrated to HIV data indicating increasing HIV prevalence from 2005 to 2014. Thus, findings are conditional on a growing epidemic. Furthermore, our model did not incorporate other harm reduction interventions such as needle/syringe programmes or naloxone distribution, as our focus was primarily on exploring synergies between harm reduction and HIV services, as observed through opioid agonist therapy on ART. However, provision of comprehensive harm reduction services and scale-up of needle/syringe programmes is urgently required in Tijuana to prevent HIV and HCV [54,55]. Lastly, our results did not incorporate potential benefits of prevention interventions on transmission to non-injecting sexual partners, which would increase impact. Box 2 outlines the research agenda for integrating opioid agonist therapy with HIV treatment services.

Box 2. Research Agenda of Integrating Opioid Agonist Therapy with HIV Treatment Services

- Modelling and economic analyses can elucidate the most efficient way to allocate resources across harm reduction and HIV treatment and prevention services to maximize health gains. Further work is needed to include additional synergistic benefits on other outcomes such as hepatitis C virus (HCV).
- Similarly, modelling can estimate the synergistic impact of structural interventions, such as drug law reform and police education programmes to align policing with public health. These programmes could further improve referral to opioid agonist therapy and ART, reduce incarceration of PWID, and reduce injection risk among PWID, further enhancing HIV and overdose prevention efforts.
- Our data indicate exposure to compulsory abstinence programme is associated with receptive syringe sharing and overdose. Further research is warranted to understand whether there is also an interaction between compulsory abstinence programmes and other HIV risks or ART provision.
- Despite the potential benefits of an integrated strategy to address HIV and broader health harms among PWID, numerous challenges exist to its implementation. Research on interventions addressing economic and stigma-related barriers to HIV prevention, care and treatment are warranted.
- Full integration of ART and opioid agonist therapy services will require changes to how ART is currently accessed and greater coordination between opioid agonist therapy and HIV providers. Service delivery questions will need to be addressed through health system research.

5 | CONCLUSIONS

Our model indicates that integrating HIV with evidence-based drug treatment services provides opportunities for synergies across multiple health outcomes affecting PWID in Tijuana. Policymakers need to understand the impact of scaling-up evidence-based programmes versus non-evidence based, especially within the context of reduced funding and drug policy reforms aligned with harm reduction. To realize the full potential of these services, structural and economic barriers will need to be removed and calls from the United Nations should be heeded to cease detainment in compulsory abstinence programmes [56].

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COMPETING INTERESTS

NM has received unrestricted research grants from Gilead and Merck unrelated to this work. All other authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

JC and NM conceptualized the study analyses and wrote the first draft of the manuscript. AB and JC developed the model. JC generated model results and figures. CM and AV conducted literature reviews to help with model parameterization. CR assisted with modelling compulsory abstinence programmes. GR, MEM and SS analysed the results and aided in manuscript drafting. All authors critically reviewed and approved the manuscript for submission.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Schematic of extensions to model by Borquez et al. Red shaded compartments display HIV disease progression and recruitment onto ART; orange shaded compartments display recruitment onto/off opioid agonist therapy; blue shaded compartments display movement between incarcerated states.

Figure S2. Proportion of PWID on antiretroviral therapy (ART). ART was assumed to have been available in 2003 and was calibrated to vary uniformly between 2% and 18% in 2012. 95% uncertainty bounds are represented by the grey shaded region.

Figure S3. Median and 95% uncertainty interval of base case model projections of HIV prevalence **(A)** overall; **(B)** among male PWID only; **(C)** and among female PWID only. Solid lines represent median and dashed lines represent 95% uncertainty interval bounds. Red triangle denotes calibration point and error bars represent 95% confidence intervals.

Figure S4. Median and 95% uncertainty interval of base case model projections of HIV incidence **(A)** among male PWID only; **(B)** and among female PWID only. Solid lines represent median and dashed lines represent 95% uncertainty interval bounds. Red triangle denotes calibration point and error bars represent 95% confidence intervals.

Figure S5. Proportion of PWID on opioid agonist therapy **(A)** or compulsory abstinence programmes **(B)** after scale-up starting in 2020.

Figure S6. Scatterplot of impact of each simulation compared to the status quo scenario for **(A)** HIV cases averted and **(B)** fatal overdoses averted from 2020 to 2030.

Figure S7. Results from sensitivity analyses showing relative change in median proportion of new HIV infections and overdoses averted compared to the scenario with full benefits of OAT on HIV and overdose outcomes **(A)** and compulsory abstinence programme (panel B). In **(A)**, duration of OAT was varied from six months (short duration) to two years (long duration) and the effect of OAT was increased or decreased to the upper and lower bounds of the 95% confidence limits of parameter values for its effect on reducing both HIV transmission and fatal overdose. Similarly, in **(B)**, the effect of the compulsory abstinence programme was increased or decreased to the upper and lower bounds of the 95% confidence limits for its effect on increasing risk of HIV transmission and fatal overdose.

Table S1. Parameters informing the HIV transmission model among PWID in Tijuana, for more details see Borquez et al

Table S2. Model calibration data among people who inject drugs in Tijuana, Mexico

Data S1. Supplementary information.

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RESEARCH ARTICLE

Integrating HIV pre-exposure prophylaxis and harm reduction among men who have sex with men and transgender women to address intersecting harms associated with stimulant use: a modelling study

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Abstract

Introduction: Among men who have sex with men (MSM) and transgender women (TW), stimulant use is high and has been associated with an increased risk of HIV infection, suicide and cardiovascular disease (CVD) mortality. We used epidemic modelling to investigate these intersecting health harms among MSM/TW in Lima, Peru and assess whether they could be mitigated by prioritizing HIV pre-exposure prophylaxis (PrEP) and harm reduction interventions among MSM/TW who use stimulants.

Methods: We adapted a dynamic model of HIV transmission among MSM/TW in Lima to incorporate stimulant use and increased HIV risk, suicide and CVD mortality. Among 6% to 24% of MSM/TW using stimulants (mostly cocaine), we modelled an increased risk of unprotected anal sex (RR = 1.35 [95%CI: 1.17 to 1.57]) obtained from local data, and increased risk of suicide (SMR = 6.26 [95%CI: 2.84 to 13.80]) and CVD (SMR = 1.83 [95%CI: 0.39 to 8.57]) mortality associated with cocaine use based on a global systematic review. We estimated the proportion of health harms occurring among MSM/TW who use stimulants in the next year (01-2020/01-2021). We also investigated the 10-year impact (01-2020/01-2030) of: (1) PrEP prioritization for stimulant-using MSM/TW compared to random allocation, and (2) integrating PrEP with a theoretical intervention halving stimulant-associated risk.

Results: MSM/TW in Lima will experience high HIV incidence, suicide mortality and CVD mortality (1.6/100 py, and 0.018/100 py, 0.13/100 py respectively) in 2020. Despite stimulant using MSM/TW comprising an estimated 9.5% (95%CI: 7.8 to 11.5) of all MSM/TW, in the next year, 11% (95%CI (i.e. 2.5% to 97.5% percentile): 10% to 13%) of new HIV infections, 39% (95%CI: 18% to 60%) of suicides and 15% (95%CI: 3% to 44%) of CVD deaths could occur among this group. Scaling up PrEP among all stimulant using MSM/TW could prevent 19% (95%CI: 11% to 31%) more HIV infections over 10 years compared to random allocation. Integrating PrEP and an intervention to halve stimulant-associated risks could reduce new HIV infections by 20% (95%CI: 10% to 37%), suicide deaths by 14% (95%CI: 5% to 27%) and CVD deaths by 3% (95%CI: 0% to 16%) over a decade.

Conclusions: MSM/TW who use stimulants experience a disproportionate burden of health harms. Prioritizing PrEP based on stimulant use, in addition to sexual behaviour/gender identity criteria, could increase its impact. Integrated substance use, harm reduction, mental health and HIV care among MSM/TW is needed.

Keywords: men who have sex with men; transgender women; stimulants; HIV pre-exposure prophylaxis; suicide; modelling

Additional Supporting Information may be found online in the Supporting Information tab for this article.

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1 | INTRODUCTION

Globally, HIV prevalence among men who have sex with men (MSM) and transgender women (TW) is 19 [1,2] and 49-fold [3] higher, respectively, than the general population. Substance use, and in particular stimulant use, is also higher among MSM and TW in a range of settings [4]. Understanding the role of substance use in HIV risk and other associated health

harms, including overdose, accidental injuries, mental health disorders and cardiovascular diseases (CVD) [5], is key to developing an integrated public health response to multiple intersecting epidemics.

Stimulants, such as cocaine and meth/amphetamines cause euphoria, sociability and energy [5], and can increase sexual desire, pleasure, prolong sexual performance and decrease sexual inhibition and pain sensation during anal intercourse [6-9]. As such, they are used by MSM and TW in a range of sexual contexts, including sex with intimate or casual partners, group sex or sex work. While causality is not well established, engagement in stimulant use and higher risk sexual behaviours are considered to co-occur within these broader risk environments [10]. In particular, stimulant use has been associated with unprotected anal sex and with HIV infection [6,11-15].

In addition to elevated HIV risks, global systematic reviews reveal a substantially elevated overall mortality among people who use cocaine or meth/amphetamines [16]. Higher suicide, overdose [17-19], CVD [20,21], accidental injuries [22] and homicide related mortality [23], contribute to this higher overall mortality. Among MSM and TW, stimulant use has been associated with suicide ideation and attempt [24-27], supporting these global findings. The lifetime prevalence of suicide attempt among MSM is estimated at between 20% and 30% (fourfold higher than among heterosexual males) [28-32]. Among TW, estimates vary between 25% and 51% [31,33-36]. Additionally, mounting evidence indicates an increased risk of CVD among sexual minorities, with stimulant use contributing to this excess risk [37-41].

While there are no approved medications to treat either cocaine or meth/amphetamine dependence [42], harm reduction can be achieved through the provision of condoms [43], HIV [44] and STI [45] pre-exposure prophylaxis (PrEP), counselling and pharmacological treatment of mental health disorders [46,47], and safe drug use and nutrition interventions to prevent overdose, accidental injuries and CVD.

Epidemic modelling can be used to quantify the contribution of groups to intersecting epidemics, and the potential population-level impact of interventions, thereby guiding evidence-based policymaking [48]. As in most Latin American countries, the HIV epidemic in Peru is concentrated among MSM and TW (13% and 27% prevalence in Lima respectively) and the country is currently considering providing HIV PrEP for these groups through the public health system. Peru is a major producer of cocaine and, in Lima, 6% to 24% of MSM/TW (varying by group) report stimulant use (mostly cocaine) in the past 3 months. We used a dynamic epidemic model to quantify the intersecting burden of stimulant use and HIV transmission, suicide and CVD mortality among MSM and TW in Lima [49], and to estimate the impact of PrEP prioritization by stimulant use and of PrEP integration with harm reduction services.

2 | METHODS

2.1 | Mathematical model

We modified a previously published epidemic model of HIV transmission among MSM and TW in Lima, Peru [49], to incorporate stimulant use, as well as explicitly represent mortality from suicide and CVD. The model is described elsewhere [49], but in brief, it considers differences in sexual behaviours based on sexual orientation, gender identity and engagement in sex work through explicitly representing four groups: homosexual self-identified MSM, heterosexual/bisexual self-identified MSM, male sex workers (MSW) and TW (including those who engage in sex work). Differences in the type of sexual partners (regular, casual and commercial) and condom use and sexual positioning by type of partner among each group are represented. The model is then further disaggregated by stimulant use (yes/no), with differential prevalence of stimulant use by group, differential frequency of unprotected anal sex by stimulant use, and differential suicide and CVD mortality rates by stimulant use. Due to a lack of data on stimulant use trajectories specifically among MSM/TW, for the baseline model we assume MSM/TW enter as either using stimulants or not, and remain in these groups, but we explore turnover in a sensitivity analysis.

2.2 | Model parameterization

The model was mainly parameterized using data from multiple local MSM/TW surveillance rounds, local epidemiological studies and global reviews and meta-analyses. Regarding stimulant use, the 2011 surveillance round among MSM/TW is the most recent source of comprehensive drug use and sexual behaviour data among MSM/TW in Peru. Using these data, we calculated the prevalence of stimulant use in the past 3 months in each group in Lima, corresponding to 6.2% (95%CI: 4.6 to 7.8) among homosexual identified MSM, 13.3% (95%CI: 10.6 to 16.1) among heterosexual/bisexual identified MSM, 23.61% (95%CI: 20.7 to 26.5) among MSW and 17.8% (95%CI: 14.3 to 21.4) among TW. Virtually all MSM/TW (98%) who reported stimulant use were using cocaine and/or cocaine paste (see Appendix S1) and therefore we used estimates of health harms associated with cocaine use for all our analyses.

2.2.1 | Stimulant use and unprotected anal sex

We used the 2011 surveillance data to estimate the pooled relative risk between stimulant use and unprotected anal sex with MSM/TW using log-binomial regression, corresponding to 1.35 (95%CI: 1.17 to 1.57) (see Appendix S1, Table S1a).

2.2.2 | Stimulant use and mortality associated with suicide and CVD

Estimates of suicide mortality among MSM/TW are not available and inferring these from data on suicide attempt and ideation would be highly uncertain. We therefore applied the crude mortality rate (CMR) associated with suicide among people who use cocaine obtained from a recent global systematic review [5] (0.07/100 person years (95%CI: 0.04 to 0.10)), to all MSM/TW, but explored higher rates based on suicide attempt estimates in sensitivity analyses. Among MSM/TW who do not use stimulants, we divided it by the standardized mortality ratio (SMR) for the increased risk of suicide among people who use cocaine, also obtained from the literature review (6.26 (95%CI: 2.84 to 13.80)) [5]. Similarly, due to lack of MSM/TW-specific data, we used the CMR and SMR associated with CVD mortality among people who use cocaine from the global review [5] (CMR: 0.13/100 person years (95%CI: 0.07 to 0.24), SMR: 1.83 (95%CI: 0.39 to 8.57)) [5]. To represent uncertainty in the CMR and SMR values for suicide and

CVD, we sampled from the 95% confidence interval values using the lognormal distribution.

2.3 | Model calibration

The HIV epidemic (and mortality from suicide and CVD) was simulated with 10,000 different parameter sets randomly sampled through Latin hypercube sampling. The log likelihood of each simulated epidemic trajectory was calculated based on time series HIV prevalence data from 1985 to 2011 for the total MSM/TW population and for each group (39 data points overall), time series HIV incidence data from 1999 to 2014 for the total MSM/TW population (5 data points), the proportion using stimulants per group in 2011 and the total ART coverage for 2011 (see Appendix S1 for full detail on parameter estimates and calibration data). Fits with a log likelihood above the 99th percentile were selected for the analysis.

2.4 | Contribution of MSM/TW who use stimulants to HIV incidence and suicide and cardio-vascular disease mortality

We used our calibrated model fits to predict HIV incidence, prevalence and mortality associated with suicide and CVD among MSM/TW in Lima for 2020. To estimate the excess burden of HIV incidence among MSM/TW who use stimulants, we calculated the proportion of new HIV infections estimated to occur among this group in 2020 and divided it by the proportion of the total MSM/TW population who use stimulants. We similarly estimated the excess burden of suicide and CVD mortality among MSM/TW who use stimulants.

2.5 | PrEP allocation by stimulant use

We assumed PrEP effectiveness of 80% [50,51] across groups assuming a distribution into three adherence groups: 84% in the high, 8% in the medium and 8% in the low adherence groups (with 90%, 50% and 20% adherence respectively). In the model when a person enters PrEP, they remain on PrEP until they exit the model and new people enter PrEP (or not) at each time step based on whether the intended coverage in a specific group is achieved. We compare the impact of prioritizing PrEP to all MSM/TW who use stimulants versus allocating PrEP independently of stimulant use in each of these groups (called "random allocation" hereafter). In the PrEP prioritization scenario, we simulated 100% PrEP coverage among HIV susceptible MSM/TW who use stimulants, varying between approximately 6% and 24% depending on the group and 0% coverage among MSM/TW who do not use stimulants. In the random allocation scenario, the same proportion from each group was covered by PrEP, reproducing PrEP coverage per group in the prioritization scenario, but it was allocated proportionally among MSM/TW who use stimulants and those who do not.

Scenario 1 (PrEP prioritization by stimulant use): $\varsigma_{k,2}(t) = 1$
$\varsigma_{k,1}(t) = 0$

Scenario 2 (Random PrEP allocation): $\varsigma_{k,f}(t) = X^1_{k,2} \Big/ \sum_f X^1_{k,f}$ corresponding to the proportion using stimulants in each group.

Where $\varsigma_{k,f}(t)$ is the PrEP coverage at time point (t) among those in sexual behaviour group k and stimulant use group f (1: no stimulant use; 2: stimulant use) and $X^1_{k,f}$ corresponds to the number of susceptible individuals in each sexual behaviour/stimulant use group.

2.6 | Harm reduction intervention(s)

Due to a lack of effective treatment for stimulant use, we simulated the potential benefits of a hypothetical harm reduction intervention package assumed to reduce the excess risks of HIV, suicide and CVD mortality associated with stimulant use by half. This could be as a result of decreases in the intensity/frequency of stimulant use or through combined harm reduction interventions including condom use distribution and promotion, psychological/psychiatric treatment to prevent suicide and CVD treatment to prevent CVD mortality.

2.7 | Sensitivity analyses

2.7.1 | PrEP adherence and stimulant use

While evidence is mixed [52], some studies have found lower adherence to PrEP among MSM/TW who use stimulants compared to those who do not [53,54]. Among MSM/TW participating in the recent iPrEX open label extension study, MSM/TW with moderate to heavy cocaine use had 2.32 greater odds of having levels of tenofovir below the level of quantitation compared to MSM/TW with no cocaine use [53]. We therefore performed a sensitivity analysis using a greater proportion of stimulant users in the low adherence group (73%, 8% and 19% in the high, medium and low adherence groups, respectively, details in Appendix S1).

2.7.2 | Duration of stimulant use

We performed a sensitivity analysis assuming turnover between groups using and not using stimulants, with an average duration of stimulant use of 5 years.

2.7.3 | Suicide rates among MSM and TW

We assumed a two to sevenfold higher rate of suicide among MSM (compared to general population) and a one to threefold higher rate among TW compared to MSM, to acknowledge evidence of higher suicide rates among these populations.

2.7.4 | PrEP prioritization by gender identity/sexual behaviour

We implemented a scenario in which 100% of TW would be covered, with the remainder given to MSW to compare the effectiveness of this established strategy to that of PrEP prioritization by stimulant use.

3 | RESULTS

3.1 | Model predictions of HIV, suicide, CVD mortality burden among MSM/TW by group

Our model estimates MSM and TW in Lima experience a high burden of HIV incidence, suicide mortality and CVD mortality, with estimates of 1.63 per 100 person-years (/100 py) (95%

Confidence Interval (2.5 and 97.5 percentiles): 0.83 to 2.51), 0.018/100 py (95%CI: 0.008 to 0.040) and 0.13/100 PY (95%CI: 0.03 to 0.5), respectively, in 2020.

The burden of each of these health harms differs by group, with 7.1% (95%CI: 4.7 to 10.0), 5.6% (95%CI: 3.6 to 8.7) and 4.7% (95%CI: 3.3 to 7.1) of new HIV infections, suicide deaths and CVD deaths, respectively, occurring among TW when they comprise 4.5% (95%CI: 2.9% to 6.7%) of the total MSM/TW population and 12.4% (95%CI: 8.7 to 16.9), 12.2% (95%CI: 4.2 to 22.9) and 9.0% (95%CI: 3.3 to 17.2) of new HIV infections, suicide deaths and CVD deaths, respectively, occurring among MSW when they comprise 8.3% (95%CI: 3.4% to 15.0%) of the total MSM/TW population. The ratios of the proportion of HIV infections, suicides and CVD deaths among each group in one year divided by the proportion of individuals in each group are shown in Figure 1, with ratios >1 indicating a disproportionate burden of infections/deaths. Our analysis indicates that MSW and TW are particularly disproportionately affected by HIV, suicide and CVD mortality.

3.2 | Model predictions of HIV, suicide and CVD mortality burden among MSM/TW who use stimulants

Our modelling indicates that despite MSM/TW who use stimulants comprising an estimated 9.5% (95%CI: 7.8 to 11.5) of the overall MSM/TW population in Lima, between 2020 and 2021, 11% (95%CI: 10% to 13%) of new HIV infections, 39% (95%CI: 18% to 60%) of suicides and 15% (95%CI: 3% to 44%) of CVD deaths would occur among this group. The ratios of the proportion of HIV infections, suicides and CVD deaths among MSM/TW who use stimulants by the proportion of MSM/TW in this group are shown in Figure 2. The median ratios for all health outcomes (HIV incidence, suicide, CVD mortality) are all> 1 indicating a disproportionate burden, with some simulations for CVD < 1, reflecting the wide uncertainty interval of the SMR for CVD associated with cocaine use (which straddles 1).

3.3 | Impact of prioritization of PrEP to MSM/TW who use stimulants

Scaling up PrEP among all (100%) MSM/TW who use stimulants in each group between 2020 and 2030 would prevent 17.9% (95%CI: 9.1 to 34.9) of new HIV infections (Figure 3). In contrast, covering the same proportion of susceptible individuals in each group, but randomly allocating to MSM/TW who use and do not use stimulants would prevent 14.9% (95%CI: 7.4 to 30.2) of new infections across a decade. Consequently, PrEP prioritization for stimulant users could prevent 19% (95%CI: 11 to 31) more new HIV infections compared to random allocation across a decade.

3.4 | Impact of integrated PrEP and harm reduction interventions for MSM/TW who use stimulants

Scaling up PrEP among MSM/TW who use stimulants in combination with harm reduction interventions that reduce the excess risk of unprotected anal sex, suicide mortality and CVD mortality associated with stimulant use by 50%, would avert 20% (95%CI: 10% to 37%) of new HIV infections, 14% (95%CI: 5% to 27%) of suicide deaths and 3% (95%CI: 0% to 16%) of CVD deaths between 2020 and 2030 (Figure 3). The proportion of new HIV infections, suicide deaths and CVD deaths that would occur among

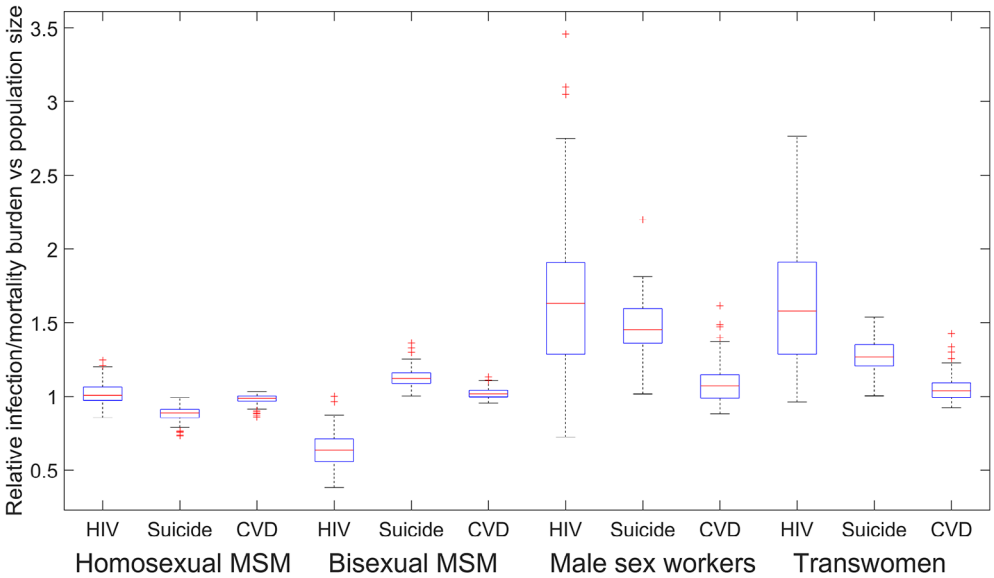

Figure 1. Ratio of the proportion of new HIV infections, suicide deaths and CVD deaths in each group and the proportion of the total population in each group in 2020 in Lima.

A ratio of >1 indicates more than the expected proportion of infections/deaths in each group, based on population size. Red lines denote median values, boxes denote 25% to 75% confidence intervals, whiskers denote minimum and maximum values not considered as outliers, and dots denote outliers. CVD, cardiovascular disease; MSM, men who have sex with men.

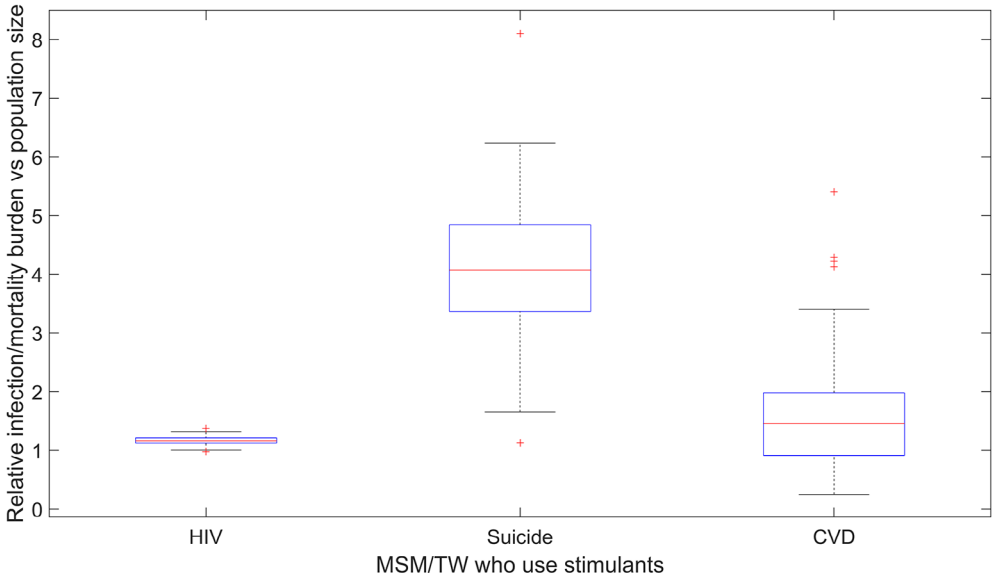

Figure 2. Ratio of the proportion of new HIV infections, suicide deaths and CVD deaths among MSM/TW who use stimulants and the proportion of the total population in this group in 2020 in Lima.
A ratio of >1 indicates more than the expected proportion of infections/deaths among stimulant using MSM/TW, based on the population size. Lines denote median values, boxes denote 25% to 75% confidence intervals, whiskers denote minimum and maximum values not considered outliers, and dots denote outliers. CVD, cardiovascular disease; MSM, men who have sex with men; TW, transgender women.

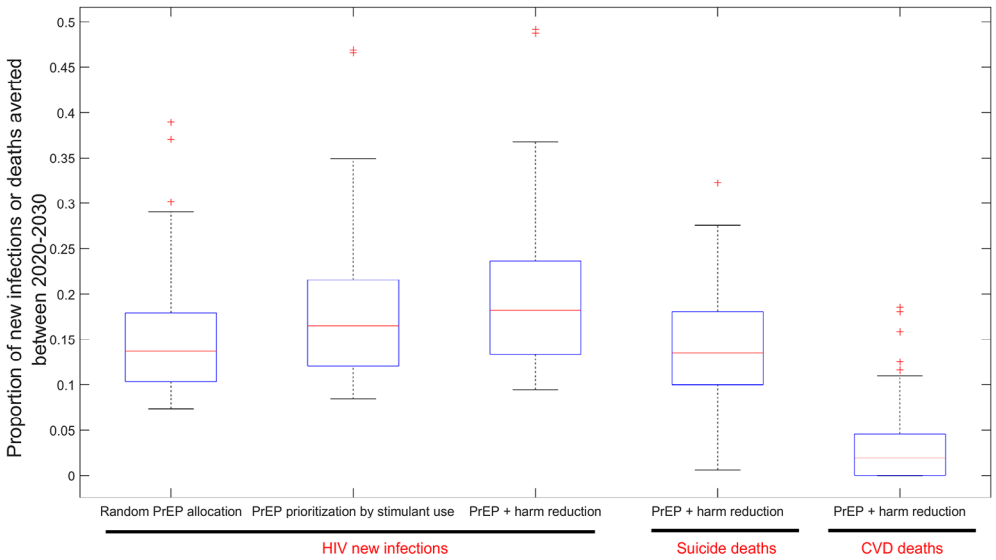

Figure 3. Proportion of HIV new infections, suicide and cardio-vascular disease (CVD) deaths averted among all men who have sex with men and transgender women under the different intervention scenarios.
PrEP, pre-exposure prophylaxis.

MSM/TW who use stimulants over 10 years in this scenario would be 5% (95%CI: 2% to 8%), 29% (95%CI: 14% to 48%) and 13% (95%CI: 3% to 32%) respectively. This indicates that while PrEP in combination with harm reduction interventions could reduce HIV incidence among MSM/TW who use stimulants to a level below that among MSM/TW who do not, a more intensive intervention would be needed to eliminate both the excess suicide and CVD mortality in this group.

3.5 | Sensitivity analyses

In the sensitivity analyses, with lower adherence to PrEP among MSM/TW who use stimulants, prioritization of PrEP to stimulant users was still more effective compared to random allocation (11% (95%CI: 3% to 22%) more effective, compared to 19% (95%CI: 11% to 31% with no adherence differences).

Assuming a five-year duration of stimulant use, the proportion of new HIV infections occurring among MSM/TW who

use stimulants was virtually unchanged at 11.1% (95%CI: 9.7% to 13.3%) and the relative increased impact of the PrEP prioritization scenario was 17% (95%CI: 9% to 31%) under this shorter duration of stimulant use (vs. 19% (95%CI: 11% to 31%) at baseline), indicating a strategy of prioritization by stimulant use may be slightly less effective under shorter durations of stimulant use.

Assuming higher suicide rates among MSM (two to sevenfold) and TW (one to threefold higher than among MSM), translated to a suicide incidence of 0.08/100 py (95%CI: 0.02 to 0.19) versus 0.018/100 py (95%CI: 0.008 to 0.040 at baseline; with 10.9% (95%CI: 4.8% to 18.4%) of suicide deaths (vs. 5.6% (95%CI: 3.6% to 8.7%) at baseline) occurring among TW (see boxplot of relative suicide burden by group in Appendix S1).

A PrEP prioritization strategy based on gender identity/sexual behaviour led to a 22% (95%CI: 9% to 41%) reduction in new HIV infections between 2020 and 2030, which is 23% greater than obtained through the prioritization strategy based on stimulant use.

4 | DISCUSSION

Our study quantified the burden of HIV, suicide mortality and CVD mortality in association with stimulant use among MSM and TW in Lima, Peru. We chose Peru as a useful case study due to the high prevalence of HIV and stimulant use among MSM and TW, comparable to other global settings. We found that MSM/TW who use stimulants are disproportionately affected by incident HIV infection, suicide mortality and CVD mortality. In addition, male sex workers and TW had a higher burden of these health harms compared to homosexual and heterosexual/bisexual MSM (who do not engage in sex work) due to increased sexual risk behaviours and stimulant use. Indeed, substance use among TW in Lima has been described [55,56] as part of the practice of street sex work, to cope with violence, hunger and long hours standing at a corner, highlighting the need to account for multiple intersecting risks within a broader context of vulnerability (see Box 1).

Our modelling indicates that PrEP prioritization for MSM/TW who use stimulants could increase its impact in Lima, even with potentially lower PrEP adherence among this group. In practice, this would entail integrating substance use and sexual risk assessment within one clinical visit when prescribing PrEP, which currently does not happen systematically. More importantly, even when questions on substance use are asked, this information is rarely acted upon, meaning that referral to substance use counselling, treatment, or harm reduction strategies are not delivered. In this study, we also showed that providing harm reduction interventions in combination with PrEP among MSM/TW who use stimulants would result in substantial overall reductions in HIV, suicide and CVD mortality. Our sensitivity analysis showed that given higher HIV incidence among TW and MSW, a PrEP prioritization strategy based on gender identity/sexual behaviour would have a larger impact compared to a prioritization strategy by stimulant use, but overall our study suggests that stimulant use should be included as an additional criterion in current guidelines [57] (see Box 1). Importantly, we assume the same PrEP adherence across groups, which would likely require increased adherence support among TW, given lower adherence among this group in the IPrEX trial [58].

To our knowledge this is the first modelling study examining the impact of stimulant use among MSM/TW on HIV, suicide and CVD, but it supports recent modelling highlighting the excess risks of stimulant use on HIV and related infections

Box 1. Policy Implications of integrating the HIV and harm reduction responses on HIV and stimulant use associated mortality among MSM and TW in Lima, Peru

- **Assess excess risk of substance use and multiple health harms among MSM/TW beyond HIV.** In addition to their excess risk of HIV compared to the general population, MSM and TW in Lima have a higher prevalence of stimulant use and are at increased risk of multiple associated health harms including suicide and CVD mortality. Considering these health harms when assessing the health of MSM/TW would lead to pertinent referrals.
- **Address excess risk of multiple health harms among MSM/TW who use stimulants.** MSM and TW who use stimulants are at increased risk of multiple health harms including HIV infection, suicide and CVD mortality compared to those who do not use stimulants. Incorporating sensitive substance use screening in the context of HIV testing, prevention and care among MSM/TW to facilitate their access to harm reduction interventions could effectively reduce both HIV transmission and mortality from suicide and CVD.
- **Prioritize pre-exposure prophylaxis (PrEP) among MSM/TW who use stimulants.** Given higher engagement in HIV associated risk behaviours among MSM/TW who use stimulants, prioritizing PrEP among this group could increase its impact on reducing overall HIV incidence among MSM/TW. Our modelling indicates that this would still be valid if stimulant use was associated with lower PrEP adherence, although this depends on baseline adherence levels and is therefore setting specific.
- **Recognize heterogeneities in HIV risk, stimulant use and associated health harms among MSM/TW.** In Lima, TW and male sex workers had both higher engagement in HIV risk behaviours and higher prevalence of stimulant use. Identifying and addressing vulnerabilities beyond HIV risk, including suicide and CVD mortality, on the basis of gender identity and engagement in sex work is important when planning the design of integrated services. Considering the broader risk environment is key.

Box 2. Research Agenda of Integrating HIV prevention and harm reduction services in Peru

- Our data indicate stimulant use is associated with unprotected anal sex. Further modelling analyses should incorporate associations between stimulant use and other HIV risk behaviours, including number of sexual partners, frequency of sex and contact with partners at higher risk of HIV to more comprehensively represent HIV risk associated with stimulant use.
- Globally, disaggregated data by sexual orientation and gender identity are missing for most health outcomes including suicide and CVD mortality. Given evidence on higher prevalence of major depressive episodes and suicide ideation and attempt among MSM and TW in particular, research that quantifies excess suicide mortality among these populations is needed.
- Increased risk of suicide and CVD among HIV-positive individuals has been documented in some settings. Further modelling analyses should evaluate the impact of such patterns on CVD and suicide mortality rates among HIV-positive MSM/TW in Peru.
- Other health outcomes associated with stimulant use and with gender identity or sexual orientation such as depression, psychosis, sexually transmitted infections, fatal accidental injuries and violence, were not explored in this analysis and warrant inclusion in modelling studies in order to provide a complete picture of multiple intersecting health harms in this population. When data are available, applying individual based modelling approaches could better represent risk heterogeneities for multiple health harms.
- PrEP scale up is at an early stage in Peru and despite the potential benefits of prioritizing it to MSM/TW who use stimulants, reaching and retaining them in PrEP might present challenges. Further research is needed to better understand PrEP engagement patterns among MSM/TW in Peru.
- While there is no proven effective treatment to reduce stimulant use, multiple interventions are available to reduce harms associated with stimulant use. Explicitly modelling these different intervention packages and associated costs would allow to identify cost effective strategies to inform the implementation of integrated services for MSM/TW in Peru.
- The feasibility of providing integrated health services among MSM/TW in Peru, that address sexual health, mental health and substance use will need to be assessed in order to identify barriers and devise solutions.

among PWID [5]. The estimated relative burden of HIV incidence among MSM/TW who use stimulants (18% (95%CI: 0% to 37%) higher) was low in comparison to findings from observational studies in other settings [11], although most have focussed on meth/amphetamines, which might have a stronger effect than cocaine on sexual risk behaviours [5]. The relative risk of unprotected anal intercourse among stimulant using MSM/TW in our sample is low compared to other settings and we did not assume any other differences in sexual behaviours (for example number of partners) by stimulant use [11,59] potentially leading to conservative estimates (see Box 2). No other modelling studies have explored PrEP prioritization by stimulant use, but findings will vary between settings depending on baseline levels of adherence and therefore similar modelling exercises should be undertaken to inform local decision making (see Box 2).

Our study has limitations. First, like all models ours was limited by data uncertainties. For example we lacked MSM/TW and setting-specific data on suicide and CVD mortality overall and by stimulant use. As a result, our model might underestimate overall infection/mortality burden and dilute differences between groups. While we implemented a sensitivity analysis to address this in relation to suicide rates, the study should be updated when MSM/TW-specific data become available (see Box 2). Importantly, the latest available HIV surveillance data among MSM/TW in Lima is from 2011. A new surveillance round was implemented in 2019, but findings are not yet published, and the sampling methodology differed from previous rounds, affecting comparability. In addition, a public sector PrEP demonstration study (i.e. ImPrEP) is ongoing in Peru and will provide empirical data to strengthen modelling to benefit prioritization strategies. Due to a lack of sexual network data, we use a compartmental model that does not fully represent the sexual network structure and its potential effect on both HIV transmission and intervention impact.

Second, we simulated a theoretical intervention package as there are no effective pharmacotherapies for stimulant use, and psychosocial therapies have weak or nonspecific effects. Our study therefore presents the potential impact if a stimulant use treatment were developed, or if a package of interventions were provided to address HIV, suicide and CVD among MSM/TW who use stimulants. Studies have shown low to moderate effectiveness of psychosocial interventions including motivational interviewing, contingency management and cognitive behavioural therapy, on reducing both methamphetamine use and risky sexual behaviours among MSM [42]. Among TW, hormonal therapy, body enhancement modifications and sexual reassignment surgeries (when needed) improves psychological outcomes [60]. A recent review recommended incorporating community-based and harm reduction interventions to these modalities to enhance impact [61]. During the past years, the Ministry of Health in Peru has sought to move mental health from specialized services towards primary care and community-based services, passing a new Mental Health Law in 2019 [62]. Mental health providers have been trained to focus on the intersection between substance use and sexual orientation/gender identity, aiming to reach MSM and TW [63]. Decreased access to healthcare across public services [64] and among MSM/TW [65] may impair success, so involving community-based organizations in intervention delivery would help address some of these issues (See Box 1).

Third, while our model incorporates much complexity in terms of sexual behaviours and stimulant use by sexual orientation, gender identity and engagement in sex work; a full range of intersecting health risks exists that we did not explore. Associations between HIV infection and suicidality have been consistently reported. Similarly, there is evidence for higher risk of CVD among HIV-positive patients [66-68]. Additionally, a range of nonfatal harms are associated with both stimulant use and HIV, including increased incidence of STI and depression [69,70]. Further epidemic modelling of the impact of stimulant use and these intersecting risks among key populations at risk of HIV is warranted (see Box 2).

5 | CONCLUSIONS

Our modelling indicates that prioritization of HIV PrEP among MSM/TW in Lima who use stimulants could enhance PrEP prioritization strategies based on sexual behaviours, or sexual orientation/gender identify. Stronger integration of interventions that address stimulant use among MSM/TW in HIV programmes is key to reducing multiple associated harms among this population. Importantly, these interventions should be complementary to broader interventions addressing the vulnerabilities and structural gaps that affect the wellbeing of sexual minorities in Peru. Interventions to guarantee their fundamental rights, including the right to an official identification reflecting their gender, the right to protection from harassment and violence, and the right to employment and health, are key to reducing persistent health disparities.

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COMPETING INTERESTS

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AUTHORS' CONTRIBUTIONS

AB and NM conceptualized the study analyses and wrote the first draft of the manuscript. AB developed the model and generated model results and figures. LT, LD, RM, SK and MF conducted the systematic reviews and meta-analyses to inform model parameterization. RA provided data to inform the model and provided guidance in its analyses and interpretation of results. KR and KK conducted statistical analyses to inform the model parameterization. CC, AS and JC aided in manuscript drafting. All authors critically reviewed and approved the manuscript for submission.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:
Appendix S1. Model specifications, equations, parameterization and analyses.

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VIEWPOINT

A call to action: strengthening the capacity for data capture and computational modelling of HIV integrated care in low- and middle-income countries

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Remarkable advances in HIV prevention, care and treatment, made through the discovery of antiretroviral drugs, have enabled people living with HIV (PLHIV) to live longer lives [1]. Yet, as they age, PLHIV experience co-morbidities that require medical care, especially for non-communicable diseases (NCD) of ageing such as cardiovascular disease, diabetes, cancer and depression and anxiety disorders [2,3]. However, whether and how NCD treatment for PLHIV is delivered is dependent on the existing health systems and policies in the country in which a person resides.

Many low- and middle-income countries (LMICs) have weak health systems with little or no NCD care or treatment available to all persons including PLHIV [4]. However, due to significant global investments to curb the HIV epidemic, HIV care in many LMICs, is delivered through clinics or other platforms that have well-trained health personnel to provide care, electronic medical records with modules to record the chronic treatment HIV requires, HIV specific educational programmes as well as other infrastructure to diagnose and treat HIV. While many of these HIV clinics currently focus only on HIV care and perhaps co-infections such as TB, resources could be spent to also deliver NCD care at these clinics. This type of "integrated care" would include the ability to diagnose, treat and care for comorbid NCDs in PLHIV. The term "integrated care" in this article refers to providing care for NCDs alongside HIV care at the same facility.

For integrated care to be implemented, health care personnel need to be trained and the infrastructure at the existing HIV clinics needs to be enhanced to enable diagnosis, treatment and care for NCDs in PLHIV. The NCDs covered in these clinics might be different in each country as well as in different regions of the country, depending on the burden of the specific NCDs in PLHIV. To enable integrated care, ideally each country would be able to determine its own priority NCDs for PLHIV.

The use of mathematical modelling to determine both the burden of NCDs in PLHIV in specific LMICs and the best way to deliver NCD care to PLHIV in that country, was suggested in a research agenda [5] developed through a multi-year, multi-agency, multi-LMIC project led by the US National Institutes of Health (NIH) Fogarty International Center (FIC) [6]. The project "Research to Guide Practice: Enhancing HIV/AIDS Platforms to Address Non-Communicable Diseases in Sub-Saharan Africa" (HIV/NCD Project) investigated the current landscape of integrated HIV/NCD care for PLHIV in sub-Saharan Africa [4] and developed a research agenda for integrated HIV/NCD care with both LMIC and US stakeholders such as ministers of health, implementers of health care and researchers. The research agenda prioritized the development of computational models to address areas such as: the cost and cost-effectiveness of integrated HIV/NCD care; the impact of integrated care on different diseases and various at-risk populations; the optimal approach to management of NCDs among PLHIV and how HIV and NCD care could be integrated along their care cascades – for example, how could they screen patients for hypertension and/or diabetes at the same time as HIV screening [7,8].

Computational modelling offers useful in-silico tools to address the pivotal areas reflected in the HIV/NCD Project research agenda. However, it is challenging for LMICs to develop computational models using local data and local capacity. Regarding local data, observational and experimental NCD data on PLHIV are seriously lacking in most LMICs where the existing HIV care systems do not collect or record NCD data. Collection of both HIV and NCD data needs to be implemented at the level of health records and national surveys. Infrastructure to systematically collect, manage, link and share NCD clinical data needs to be developed and enhanced. This effort is relevant to the upcoming NIH Common Fund programme, "Harnessing Data Science for Health Discovery and Innovation

in Africa" [9]. Improved data collection and sharing should follow modern data science best practice guidelines that arise from community consensus, such as the NIH guidelines [10] and the Findability, Accessibility, Interoperability and Reusability principles [11]. Protection of human data safety is important and applies to data collection, data handling, and development and application of modelling tools. Increased availability of datasets from LMICs will empower modellers to comprehensively investigate integrated care addressing locally relevant questions and using local information.

Regarding local capacity, there is a lack of mathematical modelling training in-country, with very few experts trained in mathematical modelling and even fewer trained in mathematical modelling of HIV/NCD integrated care. It is therefore important to develop mathematical modelling training programmes to train local researchers, who understand the local context, to model HIV and NCD integrated care. By training modellers in-country, the hope is that the modellers will remain in-country and will help mentor future generations. Below we discuss two types of Fogarty supported mathematical modelling training programmes, one focused on infectious disease modelling and one on HIV/NCD integrated care modelling, that we hope can inform future investments in HIV/NCD modelling training programmes in LMICs.

To begin to address the gap in modelling data and capacity for integrated care in LMICs three HIV/NCD mathematical modelling research grants were awarded by Fogarty under the HIV/NCD Project as part of a peer-reviewed competition [12]. Each of the grants had a linked capacity building component and the three grants together provided computational modelling training to six persons from Kenya and Uganda and allowed staff from local ministries to spend time with modelling experts from the US and Europe. To analyse the research capacity portion of the grants, we used WHO/ESSENCE "Seven principles for strengthening research capacity in LMICs" as a framework [13] to design a survey and follow-up interviews with modelling grantees to identify facilitators and barriers to building the capacity to construct computational models specifically applied to integrated HIV/NCD care in LMICs. The results of the surveys and interviews are detailed in Table 1 below. Several important facilitating factors were identified for building modelling capacity, for example, having established long-term partnerships with institutions and researchers in the country; holding high-income country (HIC)-led short-term training at LMIC academic institutions to capacitate the institutions and engage their support for this field; and having the HIC initially provide mentors until mentors in the LMIC can be established. Important barriers identified were the lack of trust for computational modelling among policy makers in-country; the lack of long-term institutional investment in mathematical modelling in the country, particularly as it may not be a priority scientific area for the country; unreliable internet; and a lack of recognition in both HIC and LMIC tenure track positions at academic institutions that scientific capacity building is important.

Fogarty International Center has also led modelling efforts like the Multinational Influenza Seasonal Mortality Study and the Research and Policy in Infectious Disease Dynamics programme, which have generated research activities and training workshops to build a network of global experts in infectious disease modelling [14]. Establishing a similar modelling community in LMICs focused on integrated HIV care is only starting, and, from our experiences with 136 workshops [14] we have summarized the following recommendations to strengthen and sustain progress.

1 Modellers should make modelling tools and analytic packages publicly available to wider audiences. Accessible user-friendly tools should be developed that address NCD care for PLHIV in LMICs, ideally by modellers in LMICs once capacitated. This could be achieved by modifying generic policy modelling tools such as the Spectrum software to incorporate more specific questions of interest to this region. Furthermore, existing simulation tools should be repackaged into workflows with convenient user interface, visualization components and reporting modules.

2 Like the experiences of the grantees above working on HIV/NCD integrated care, working on infectious disease modelling we have found that local training programmes should be developed at LMIC academic centres affiliated with universities to grow the next cohort of LMIC modellers [13–15]. These programmes should include master's and Ph.D. programmes in computational modelling [15]. A notable example is the South African Center for Excellence in Epidemiological Modelling and Analysis (SACEMA), a multidisciplinary research centre hosted at Stellenbosch University, focused on modelling interventions to improve health in Africa. SACEMA offers "modelling clinics" for African participants who bring a dataset and research questions for analysis in Stellenbosch, South Africa, and are encouraged to continue their modelling efforts at their home institutions [16]. SACEMA also hosts several research fellows in-residence [16].

3 We found, in our experience, that 1.5 days to 1 week-long trainings in disease modelling along with student exchanges with expert groups in HICs, are beneficial to begin to grow modelling in LMICs. However, they cannot replace formal academic training locally [14]. Although these trainings are rather short to provide extensive instruction in disease modelling, it is seen as a reasonable amount of time that students and professionals can take away from their regular duties. Short workshops can also help identify participants who are particularly interested in the field of computational modelling and can be offered further trainings and visits to HIC institutions to deepen their expertise.

4 Training of decision makers to understand model outputs, particularly uncertainty and confidence intervals, will allow them to be confident when using model estimates to make decisions and help them to trust modelling.

Computational modelling is a relatively fast, low-cost solution to answer questions about HIV/NCD integrated care, which are mentioned above and can also provide future projections useful for planning. Researchers in-country must be part of the process of developing and using models, ultimately in a leadership role, requiring training efforts to empower researchers and strengthen institutional capacity. Policy makers need to be educated about the advantages and limitations of modelling estimates to allow them to use model outputs appropriately for decision-making. Finally, collection of new

Table 1. Facilitators and barriers to computational modelling capacity building

Principles for sustainable capacity building[a]	Facilitators[b]	Barriers[b]
Network, collaborate, communicate and share experiences	New platforms developed for data collection and collaboration	1) Lack of infrastructure and funding; 2) Lack of institutional capacity in-country; 3) unreliable communications networks, especially internet communications 4) lack of modelling conferences in LMICs
Understand the local context and evaluate existing research capacity	1) Established long-term partnerships and relationships with in-country researchers; 2 ability to conduct systematic reviews	1) No existing partnerships or relationships; 2) no experience working in LMICs or in conducting reviews
Ensure local ownership and active support	1) Having in-country partners (MOH/academic) take a lead role in project; 2) leverage previous ties and relationships	1) Distrust and/or lack of understanding of modelling; 2) distrust of sharing of data outside of country; 3) high turnover in local institutions; 4) huge workloads and competing priorities of in-country partners
Build-in monitoring, evaluation and learning from the start	Other successful programmes using monitoring and evaluations and capacity building, such as HIV programmes, enable more support for this type of activity	Other more pressing priorities mean that these areas are often undervalued
Establish robust research governance and support structures and promote effective leadership	1) Funding for long-term institutional capacity building; 2) HIC mentors for leadership; 3) leadership training; 4) fellowship training at academic institutions	Lack of 1) long-term institutional investment; 2) in-country mentors; 3) licenses required for models; 4) locally relevant data; 5) recognition at the university level (HIC & LMIC) that capacity building is important thus no career credit to researchers who conduct training/capacity development
Embed strong support, supervision and mentorship structures	1) Initially some of the support and mentorship may have to come from the HIC partners; 2) short courses at institutions in-country are important to generate support	Lack of knowledge about modelling leads to lack of support in LMICs
Think long-term, be flexible and plan for continuity	1) Long-term investment either by in-country funders or external funders is necessary; 2) computational modelling career track pipeline allows for sustainability; 3) involve in-country academic institutions	Short term investments, such as workshops and short course trainings not affiliated with academic institutions in-country do not allow for sustainable capacity building

HIC, High Income Country; LMICs, Low- and middle-income countries, MOH, Ministry of Health.
[a]The seven principles for strengthening research capacity in low- and middle-income countries: simple ideas in a complex world (2014) by ESSENCE on Health Research is licensed by the Wellcome Trust of the United Kingdom under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License. (http://www.who.int/tdr/partnerships/initiatives/essence/en/);
[b]these data were collected from CRDF Global (OISE-17-62962-1, OISE-17-62965-1, OISE-17-62967-1) grantees through progress reports, a short survey and follow-up interviews.

datasets on NCDs in PLHIV in LMICs will be essential as models are only as good as the underlying data they rely on. Now is the time to invest in data integration and capacity building for mathematical modelling in LMICs to enable more science-based decisions for holistic treatment of PLHIV and the entire population.

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COMPETING INTERESTS

None of the authors have competing interests to declare.

AUTHORS' CONTRIBUTIONS

BB, CV, PB, XW and LK conceived, wrote, reviewed, read and approved the manuscript. All contributed equally. All authors have read and approved the final manuscript.

ABBREVIATIONS

PLHIV, People living with HIV; NCD, Non-communicable diseases; LMICs- Low- and middle-income countries; NIH- US National Institutes of Health; FIC, Fogarty International Center; HIC, High-income country; SACEMA, South African Center for Excellence in Epidemiological Modelling and Analysis.

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AUTHOR INDEX

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